Continuous glucose monitoring in extremely preterm infants in intensive care: the REACT RCT and pilot study of 'closed-loop' technology

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Abstract

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Background: Hyperglycaemia and hypoglycaemia are common in preterm infants and are associated with increased mortality and morbidity. Continuous glucose monitoring is widely used to target glucose control in adults and children, but not in neonates.

Objective: To evaluate the role of continuous glucose monitoring in the preterm infant.

Design: The REAl-time Continuous glucose moniToring in neonatal intensive care project combined (1) a feasibility study, (2) a multicentre randomised controlled trial and (3) a pilot of 'closed-loop' continuous glucose monitoring. The feasibility study comprised a single-centre study ($n = 20$). Eligibility criteria included a birthweight ≤ 1200 g and aged ≤ 48 hours. Continuous glucose monitoring was initiated to support glucose control. The efficacy and safety outcomes guided the design of the randomised controlled trial. The randomised controlled trial comprised a European multicentre trial ($n = 182$). Eligibility criteria included birthweight ≤ 1200 g and aged ≤ 24 hours. Exclusion criteria included any lethal congenital abnormality. Continuous glucose monitoring was initiated to support glucose control within 24 hours of birth. In the intervention group, the continuous glucose monitoring sensor provided real-time data on glucose levels, which guided clinical management. In control infants, the continuous glucose monitoring data were masked, and glucose level was managed in accordance with standard clinical practice and based on the blood glucose levels. The primary outcome measure was the percentage of time during which the sensor glucose level was within the target range of 2.6–10 mmol/l. Secondary outcome measures included mean sensor glucose level, the percentage of time during which the sensor glucose level was within the target range of 4–8 mmol/l, the percentage of time during which the sensor glucose level was in the hyperglycaemic range (i.e. > 15 mmol/l) and sensor glucose level variability. Safety outcomes included hypoglycaemia exposure. Acceptability assessment and health economic analyses were carried out and further exploratory health outcomes were explored. The mean percentage of time in glucose target range of 2.6–10 mmol/l was 9% higher in infants in the continuous glucose monitoring group (95% confidence interval 3% to 14%; $p = 0.002$), and the mean time in the target range of 4–8 mmol/l was 12% higher in this group (95% confidence interval 4% to 19%; $p = 0.004$). There was no difference in the number of episodes of hypoglycaemia.

ABSTRACT

Exploratory outcomes showed a reduced risk of necrotising enterocolitis in the intervention arm (odds ratio 0.33, 95% confidence interval 0.13 to 0.78; $p = 0.01$). Health economic analyses demonstrated that continuous glucose monitoring was cost-effective on the basis of the cost per additional case of adequate glucose control between 2.6 and 10 mmol/l. The 'closed-loop' study was a single-center pilot study, with eligibility criteria including a birthweight of ≤ 1200 g and aged ≤ 48 hours. Infants underwent continuous glucose monitoring for the first week of life ($n = 21$), with those in the intervention group receiving closed-loop insulin delivery between 48 and 72 hours of age. The primary outcome of percentage of time in the target range (i.e. sensor glucose 4–8 mmol/l) increased from a median of 26% (interquartile range 6–64%) to 91% (interquartile range 78–99%) during closed-loop insulin delivery ($p < 0.001$).

Limitations: These studies have not defined the optimal targets for glucose control or the best strategies to achieve them in these infants.

Future work: Studies are needed to evaluate the longer-term impact of targeting glucose control on clinical outcomes.

Conclusions: Continuous glucose monitoring in extremely preterm infants can improve glucose control, with closed-loop insulin delivery having further potential to target glucose levels. Staff and parents felt that the use of continuous glucose monitoring improved care and the results of the health economic evaluation favours the use of continuous glucose monitoring.

Trial registration: Current Controlled Trials ISRCTN12793535.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 16. See the NIHR Journals Library website for further project information. Medtronic plc provided some MiniMed™ 640G systems and Nova Biomedical (Waltham, MA, USA) provided point-of-care devices.

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List of abbreviations

ADE	adverse device effect	MRI	magnetic resonance imaging
AE	adverse event	NEC	necrotising enterocolitis
BPD	bronchopulmonary dysplasia	NICU	neonatal intensive care unit
CE	Conformité Européenne	NMB	net monetary benefit
CEAC	cost-effectiveness acceptability curve	OR	odds ratio
CGM	continuous glucose monitoring	PDA	patent ductus arteriosus
CI	confidence interval	POC	point of care
CONSORT	Consolidated Standards of Reporting Trials	PSS	Personal Social Services
		RCT	randomised controlled trial
CRF	case report form	REACT	REAl-time Continuous glucose moniToring in neonatal intensive care
CT	computed tomography		
DMEC	Data Monitoring Ethics Committee	ROP	retinopathy of prematurity
ECG	electrocardiography	SADE	serious adverse device effect
EEG	electroencephalography	SAE	serious adverse event
GLM	generalised linear modelling	SD	standard deviation
ICER	incremental cost-effectiveness ratio	SDS	standard deviation score
IQR	interquartile range	SE	standard error
ISO	International Organization for Standardization	TMG	Trial Management Group
		TSC	Trial Steering Committee
MHRA	Medicines and Healthcare products Regulatory Agency		

Plain English summary

Both high and low blood sugar (glucose) levels are common in preterm babies and have been linked to worse health outcomes. Managing the extremes of glucose levels is difficult as it requires frequent invasive blood sampling. In addition, every baby responds differently to treatments. In children with diabetes, who have similar difficulties, a continuous glucose monitor can be used to better target glucose levels. Continuous glucose monitoring requires a small sensor to be inserted under the skin; this can be left in place for up to a week. The REAl-time Continuous glucose moniToring in neonatal intensive care project aimed to assess whether or not continuous glucose monitoring is helpful for the management of preterm babies in intensive care. There were three parts to the project, each with protocols and patient information sheets developed with support from parents:

1. a feasibility study to guide the design of a randomised clinical trial
2. a randomised clinical trial
3. a pilot study, combining continuous glucose monitoring with computer advice (i.e. the 'closed-loop study').

The randomised clinical trial recruited 182 babies within 24 hours of their birth. A continuous glucose monitor was inserted in all babies, but doctors used the results to support sugar control in only half of the babies. The other half received standard care (continuous glucose monitor data were collected, but were not made available to the clinical team).

The study was positive in that continuous glucose monitoring helped to target sugar levels without increasing the risk of low blood sugar levels. The clinical team and parents felt that the continuous glucose monitor improved the care of babies. In health economic calculations from birth to 36 weeks' corrected gestational age, continuous glucose monitoring was, on average, less costly and more effective than standard care. The closed-loop study showed that the use of a computer, combined with continuous glucose monitoring, can further increase the time within the target sugar levels. Further studies are required to determine the ideal target for sugar levels in these babies and the impact on long-term health. A continuous glucose monitor provides the technology to support such studies.

Scientific summary

Background

Hyperglycaemia and hypoglycaemia have both been associated with increased mortality and morbidity for preterm infants. However, controversy remains regarding the optimal management. This relates to the unique challenges in the extremely preterm infant when aiming to optimise nutritional intake, while also avoiding the risks of insulin-induced hypoglycaemia. Continuous glucose monitors are widely used in adults and children with diabetes to target glucose control, and have been trialled in intensive care, but they are not approved for use in neonates. Computer algorithms are also used to guide glucose management in patients with diabetes and have been trialled in adult intensive care patients, with variable benefits. This REAl-time Continuous glucose moniToring in neonatal intensive care (REACT) project aimed to evaluate the potential role of continuous glucose monitoring to support the use of insulin and additional glucose to target glucose control in the extremely preterm infant, both alone and in combination with a bespoke computer algorithm.

Objectives

- To undertake a single-centre feasibility study of continuous glucose monitoring in preterm infants to inform the design of a multicentre randomised controlled trial.
- To evaluate the clinical role of continuous glucose monitoring in terms of efficacy, safety, utility and cost-effectiveness through a multicentre randomised controlled trial.
- To pilot the potential use of a 'closed-loop' system for glucose control using continuous glucose monitoring.

Feasibility study

Objectives
To inform the design of a multicentre randomised controlled trial through provisional assessment of accuracy, safety and utility of the intervention, and to explore the primary outcome measure of time in target (i.e. 2.6–10 mmol/l) to inform power calculations.

Methods
A single-centre study with eligibility criteria of birthweight ≤ 1200 g and aged ≤ 48 hours. The intervention lasted for up to 7 days. Infants had an Enlite™ sensor (Medtronic plc, Watford, UK) inserted in their lateral thigh and linked to a MiniMed™ Paradigm® Veo™ system (Medtronic plc). The sensor glucose data were used alongside a paper guideline to support the clinical management of glucose control. The study received all necessary ethics and regulatory approvals, and informed consent was received prior to any study interventions.

Results
Twenty-one infants were recruited and one infant was withdrawn because of failure of sensor insertion.

Accuracy
Comparative data demonstrated a mean absolute relative difference of 10% and 11% between blood glucose levels measured on the continuous glucose monitor and on the blood gas analyser and Novostat (Nova Biomedical, Waltham, MA, USA) meter, respectively.

Safety

There were no serious adverse device effects. Three infants had an episode of hypoglycaemia (i.e. blood glucose of < 2.6 mmol/l) related to the loss of intravenous access, and the infants were asymptomatic, clinically well and not on insulin. There were no concerns about skin integrity or infection at the sensor site.

Utility and staff acceptability

Nursing staff were positive about the impact on care in terms of feeling more empowered to manage the infant's glucose control and reported that the use of continuous glucose monitoring led to better care. However, staff found the use of both predictive and threshold alarms challenging. The median of the mean number of blood samples per day for an infant was 4.1 (range 3.3–4.3).

Efficacy data

Sensor data were available from 20 infants. The median percentage of time in the primary target range (i.e. 2.6–10 mmol/l) was 78% (interquartile range 59–94%) and the median percentage of time in the secondary target range (i.e. 4–8 mmol/l) was 46% (interquartile range 35–66%), with a standard deviation of sensor glucose of 2.39 mmol/l (95% confidence interval 1.78 to 3.67 mmol/l).

Conclusion

Based on the feasibility data, the standard deviation of the primary outcome (time in target range of 2.6–10 mmol/l) was conservatively estimated at 22% and, therefore, it was calculated that the sample size required to provide 90% power to detect a difference of 10%, at the 5% significance level, was 200 infants. Consensus was reached among expert opinion from the Trial Steering Committee and Data Monitoring and Ethics Committee that a 10% difference would be clinically meaningful.

Randomised controlled trial

Trial objectives

To evaluate the efficacy, safety, utility and cost-effectiveness of real-time continuous glucose monitoring in preterm infants in neonatal intensive care.

Methods

Study design

A multicentre interventional randomised controlled trial comparing the use of continuous glucose monitoring with standard clinical management of glucose control in preterm infants. Participants were recruited from 13 level 3 neonatal intensive care units across Europe. Infants were recruited within 24 hours of their birth and underwent continuous glucose monitoring for the first 6 days of life. Data were collected until 36 weeks' corrected gestational age.

Eligibility

Preterm infants were eligible for trial entry if they weighed ≤ 1200 g at birth, were aged ≤ 24 hours and ≤ 33+6 weeks gestation, and there was informed parental consent. Infants were excluded if they had a lethal congenital abnormality, any congenital metabolic disorder or no realistic prospect of survival at trial entry. Following consent, infants were randomised in a 1 : 1 ratio to either the control or the intervention arm of the study using a web-based randomisation system.

Intervention: continuous glucose monitoring with guideline

Each infant had a subcutaneous Enlite sensor inserted and linked to a MiniMed™ 640G (Medtronic plc). Clinical staff were advised to use the continuous glucose monitor glucose readings in combination with a written guideline for management of glucose control. The guideline was developed during the REACT feasibility study.

Control: standard care

Each infant had a subcutaneous Enlite sensor inserted and linked to a MiniMed™ 640G. The device collected glucose data continuously, but the display screen was masked to clinical staff. Glucose control was managed in accordance with local standard clinical care using point-of-care blood glucose monitoring.

Outcomes

The primary outcome measure was the percentage of time during which the sensor glucose level was in the target range of 2.6–10 mmol/l during the first 6 days of life.

The secondary outcome measures were categorised as efficacy, safety, acceptability or health economics outcomes, or as exploratory clinical outcomes:

- efficacy –

  - mean sensor glucose in the first 6 days of life
  - percentage of time sensor glucose is in the target range of 4–8 mmol/l within the first 6 days of life
  - sensor glucose variability within individuals, as assessed by within-patient standard deviation
  - percentage of time glucose levels are in the hyperglycaemic range (i.e. sensor glucose > 15 mmol/l)

- safety –

  - incidence of hypoglycaemia, defined as any episode of blood glucose of > 2.2 mmol/l and < 2.6 mmol/l
  - incidence of hypoglycaemia, defined as a continuous episode of sensor glucose of < 2.6 mmol/l for > 1 hour
  - incidence of hypoglycaemia, defined as any episode of blood glucose of ≤ 2.2 mmol/l

- acceptability –

  - clinical staff rating score of impact on clinical care
  - frequency of blood glucose monitoring
  - clinical use of guideline

- health economics –

  - cost-effectiveness expressed in terms of incremental cost per additional case of adequate glucose control (defined as > 80% time spent between 2.6 and 10 mmol/l)

- exploratory outcomes –

  - mortality and morbidity before 36 weeks' corrected gestational age.

An independent Data Monitoring Ethics Committee was established to review safety data from the trial and trial management was overseen by the Trial Steering Committee.

Results

A total of 182 infants were recruited to the trial. The mean time in the glucose target range of 2.6–10 mmol/l was 9% higher in infants in the continuous glucose monitoring group than in infants in the control arm (95% confidence interval 3% to 14%; $p = 0.002$). In the case of the glucose target level range of 4–8 mmol/l, the mean percentage of time in the target range was 12% higher in the intervention group (95% confidence interval 4% to 19%; $p = 0.004$). There was no difference in the number of episodes of hypoglycaemia between the arms. Exploratory outcomes showed a reduced risk of necrotising enterocolitis (odds ratio 0.33, 95% confidence interval 0.13 to 0.78; $p = 0.01$)

in the intervention arm compared with the control arm. Both staff and parents reported that the use of continuous glucose monitoring improved care and the continuous glucose monitoring was found to be dominant in health economic terms.

Conclusions

Continuous glucose monitoring in preterm infants can support the use of insulin and glucose to optimise glucose control, reducing exposure to hyperglycaemia without increasing the risk of hypoglycaemia. Staff and parents felt that the use of continuous glucose monitoring improved care. Economic evaluation demonstrated that, over the first 7 days, continuous glucose monitoring is, on average, more costly and more effective than standard care. Assuming cost-effectiveness thresholds of £1000, £5000 and £10,000, the probability of cost-effectiveness for continuous glucose monitoring reached 90% at approximately £6000, whereas the net monetary benefit associated with continuous glucose monitoring became positive at a cost-effectiveness threshold of £5000. However, in terms of clinical impact over a time horizon extending to 36 weeks' corrected gestational age, continuous glucose monitoring was, on average, less costly and more effective, and therefore dominant in health economic terms.

Closed-loop system

Objectives

Assessment of the potential for continuous glucose monitoring combined with a computer algorithm, 'closed loop', to be more effective in targeting glucose control in extremely preterm infants than the use of continuous glucose monitoring combined with a simple paper guideline.

Methods

A single-centre study with eligibility criteria of birthweight ≤ 1200 g and aged ≤ 48 hours. All infants underwent subcutaneous continuous glucose monitoring in the first week of life, with those in the intervention group receiving closed-loop insulin delivery between 48 and 72 hours of age. The primary outcome was percentage of time in target range (i.e. sensor glucose level of 4–8 mmol/l).

Results

Data from 20 infants showed the time in the target range increased from a median of 26% (interquartile range 6–64%) with paper guidance to 91% (interquartile range 78–99%) during closed-loop insulin delivery ($p < 0.001$), without increasing hypoglycaemia.

Conclusions

Closed-loop glucose control based on subcutaneous glucose measurements is feasible and has the potential to further target glucose control in extremely preterm infants.

Implications for health care

The findings of these studies demonstrate that continuous glucose monitoring in preterm infants can increase the time in the glucose target range of 2.6–10 mmol/l compared with standard clinical care. The study highlighted the challenges of using devices that are not designed for preterm infants, and the need for devices that can address the unique physiological and pathological challenges facing these infants, and the staff and parents caring for them. Robust pathways are needed to encourage the development and validation of devices for use in such vulnerable populations.

'Closed-loop' technology has the potential to provide a further personalised approach to targeting glucose control. The trial data clearly demonstrated the wide variability between infants, and it is in this context that such intelligent algorithms can help to optimise care. It could also help to address some of the challenges of providing optimal care in very busy neonatal intensive care units where it is acknowledged that there is sometimes a shortage of adequately trained nursing staff to deliver care. Importantly, despite

the potential additional workload of a clinical trial, the staff and parents reported that they felt that the use of continuous glucose monitors improved care. It will therefore be important to ensure that these devices can be introduced into clinical practice in a robust manner to ensure adequate support and training for staff so that the devices are used effectively and safely in this population.

Despite the challenges, the health economic analysis demonstrated the use of continuous glucose monitors to be favourable even over a relatively short time horizon. Exploratory analysis also showed a reduced risk of necrotising enterocolitis, but this trial was underpowered to determine the impact on other clinical outcomes, and larger studies are needed to confirm if this is a robust finding and to look at other impacts. Further studies are also needed to elucidate the optimal targets of glucose control to improve long-term health outcomes. Continuous glucose monitor technology is well placed to support such studies.

Recommendations for research

The findings of the REACT project raise the following important questions that need to be addressed in further studies.

Short term

- What is the optimal glucose target range for preterm infants at this time?
- What is the prevalence of glucose dysregulation throughout the preterm course on a neonatal intensive care unit?
- What is the role of continuous glucose monitoring in infants in the neonatal intensive care unit who are at risk of glucose dysregulation for other reasons, such as following hypoxic–ischaemic insults and during cooling?

Future

- Can we design a continuous glucose monitor that is better suited to the unique physiology and pathology of the newborn?
- Can we design 'closed-loop' systems that will support staff in further safely targeting glucose levels in these infants and save staff time?

Long term

- What is the impact of silent hypoglycaemia in preterm infants?
- What is the impact of 'optimising' glucose control in the preterm infant on health outcomes?

Trial registration

This trial is registered as ISRCTN12793535.

Funding

Chapter 1 Introduction

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Increasing numbers of infants are being born preterm. These infants require intensive care and have a high risk of early mortality and short-term morbidity.[5] Among surviving infants, the incidence of long-term health problems, including learning difficulties, is high, with significant long-term costs to the NHS and society.[6] Treatable neonatal causes of long-term health problems have been difficult to establish. National priorities for research include investigation of the management of infants who are born too early or too small, and evaluation of the reasons for variations in outcome of 'high-risk' neonates. Early postnatal glucose control may be an important and modifiable risk factor for clinical outcomes. In utero, glucose levels are normally maintained between 4 and 6 mmol/l,[7] but infants born preterm are at risk of both hyperglycaemia (20–86%, depending on how it is defined) and hypoglycaemia (17%; blood glucose level < 2.6 mmol/l).[8]

Existing research

Hyperglycaemia and hypoglycaemia in the preterm infant
Hyperglycaemia and hypoglycaemia have both been associated with increased mortality and morbidity for preterm infants.[9,10] Hyperglycaemia can lead to acute problems of persistent osmotic diuresis and metabolic acidosis, which can be difficult to control, and has been associated with increased risk of intraventricular haemorrhage.[11] Hyperglycaemia has also been associated with increased long-term morbidity, including increased risk of retinopathy of prematurity (ROP).[9,12,13] Pivotal single-centre studies in adult intensive care have demonstrated that tight glycaemic control can reduce both mortality and morbidity.[14] However, these results have been difficult to replicate because of the risk of hypoglycaemia.[15] A trial in paediatric intensive care, targeted to reduce hyperglycaemia, demonstrated a reduction in length of intensive care admission and mortality, but a significant increase in hypoglycaemia.[16] This is of particular concern as attempts to reduce the prevalence of hyperglycaemia may increase the risk of hypoglycaemia in preterm infants because of their variable sensitivity to insulin. In addition, the developing brain appears to be particularly vulnerable to both hyperglycaemic[17] and hypoglycaemic insults. A Cochrane review[9] has highlighted the need for further studies into the impact of interventions to improve glucose control in these infants.

Current glucose monitoring in neonatal intensive care
Although glucose monitoring is implemented in all very preterm infants, it is currently limited to intermittent blood sampling, with long periods when glucose levels are unknown. The reason for the intermittent nature of glucose monitoring is that current methodologies for measurement of glucose levels are dependent on blood sampling either from a central arterial line or by heel prick. The very small circulating volumes of blood in preterm infants mean that it is also important to minimise the number of blood samples and volume of blood sampled in this way. Furthermore, current practice in neonatal intensive care units (NICUs) aims to reduce the frequency of handling of infants, as this has been shown to improve outcomes.[18] By contrast, other physiological parameters, such as oxygen saturation, blood pressure and heart rate, are all monitored continuously to prevent wide fluctuations. It is increasingly thought that fluctuations in glucose levels may also have a significant impact on long-term outcomes.[19]

If clinical interventions to optimise glucose control are to be safe and effective in the intensive care setting, robust methods of monitoring glucose levels in real time need to be in place. Furthermore, to fully understand the clinical significance of hyperglycaemia and hypoglycaemia, it is imperative that robust data are available regarding their true prevalence throughout the period of intensive care. Current follow-up studies are dependent on infrequent measurements of blood glucose, typically taken for clinical reasons and with the inherent associated bias. Continuous glucose monitoring (CGM) therefore has the potential to both safely guide acute clinical management to optimise control and provide robust data on which to assess the long-term impact.

Continuous glucose monitoring

A range of technological methods have been tested for their abilities to support CGM. Currently, the only CGM method used in clinical practice for the management of patients with diabetes involves measurement of interstitial glucose levels, which are calibrated against blood glucose measurements. CGM devices comprise a disposable subcutaneous oxidase-based platinum electrode that catalyses interstitial glucose, generating an electrical signal that is transmitted to a monitor for recording or display. Three companies have devices on the market for CGM: Dexcom Inc. (San Diego, CA, USA), Abbott Laboratories UK (Berkshire, UK) and Medtronic plc (Watford, UK). However, because of the size of extremely preterm infants and issues of insertion and attachment to these small infants, only the Medtronic plc devices are currently suitable for use in the extremely preterm infant.

Although this is a rapidly changing field, early CGM devices were used to collect data in real time, but these data could be downloaded only retrospectively to be reviewed and used to guide future clinical treatment. This is useful (1) in the setting of research, (2) to provide advice on long-term behavioural or medical interventions and (3) in the case of patients with stable diabetes, to review patterns of glucose control over time. These devices have also been used in preterm infants without side effects and identified significant periods of both hyperglycaemia and hypoglycaemia that were undetected clinically.[20–22] However, they are not suitable for providing data that is useful for acute clinical management. Newer CGM devices allow the data to be viewed in real time, providing information on glucose trends, with the potential to identify episodes of hyperglycaemia and hypoglycaemia, thus allowing the possibility of earlier intervention and prevention.

Development of continuous glucose monitors

The development of CGM devices provides the opportunity for data on glucose levels to be recorded every 5 minutes and viewed continuously. A number of different devices are available for clinical use and they are increasingly found to help reduce glycated haemoglobin and glycaemic variability in patients with type 1 diabetes without increasing the risk of hypoglycaemia. These devices allow patients to monitor their glucose levels by displaying absolute glucose concentrations as well as trends. Some systems depend on intravenous access, some use microdialysis and others measure interstitial glucose levels. Their use has been trialled in adults in intensive care and in patients requiring cardiac surgery.[23] Although these studies have been limited, they have shown that the devices are accurate and safe in cardiac surgical patients and can reduce the risk of hypoglycaemia in adults in intensive care.[24] Some have raised concerns about the lack of absolute sensitivity of individual readings at glucose thresholds, emphasising the potential importance of CGM as an early-warning system for both hyperglycaemia and hypoglycaemia.[25]

These studies have highlighted the need for methodologies that can provide real-time data and allow adjustment of clinical management in the setting of a rapidly changing clinical picture of intensive care.[26,27] These benefits have been seen in the adult intensive care setting, where blood glucose levels are routinely measured much more frequently than in NICUs. Therefore, the potential for benefits in the NICU setting, where the frequency of blood glucose measurements is much lower, is likely to be more clinically significant. Key recent developments in these devices include extended sensor life, such that sensors can now remain in situ for 6 days (previously 72 hours), and changes to the sensor construction and the calibration algorithms, which have led to improved overall accuracy.[28] This is particularly important in terms of sensitivities to detect threshold levels of hypoglycaemia and hyperglycaemia.

Previous use of continuous glucose monitors in neonates

There is limited use of CGM in NICUs. We have used blinded CGM devices as part of an international multicentre trial in preterm infants and assessed the accuracy of these devices compared with current clinical practice.[29,30] These studies suggested that the value of CGM could be in providing early warning of fluctuations in glucose levels to guide the need for blood glucose assessment. In addition, by providing a continuous readout, episodes of hyperglycaemia and hypoglycaemia could be anticipated and therefore avoided. We have previously collected 'blinded' CGM data as part of the Neonatal Insulin Therapy [Nirture (Neonatal Insulin Replacement Therapy in Europe Study)] trial using a CGM (Medtronic plc)[21] and in a small feasibility study using the iPro™2 (Medtronic plc). In the small feasibility study of 10 infants with a birthweight $\leq$ 1200 g monitored from birth for up to 7 days, infants had a median gestational age at birth of 28.4 weeks and a median birthweight of 840 g. The median time in the target glucose range of 2.6–10 mmol/l was 58% and the median time in the target glucose range of 4–8 mmol/l was 40%.

The REACT project

The purpose of the REACT project was to evaluate the role of CGMs in the detection and management of hyperglycaemia and hypoglycaemia in NICUs. The project was funded by the National Institute for Health Research Efficacy and Mechanism Evaluation programme, with additional support of CGM equipment provided by Medtronic plc and sponsorship from the University of Cambridge Addenbrookes Hospital NHS Trust (Cambridge, UK). There were three stages:

1. to undertake a single-centre feasibility study to inform the design of a multicentre randomised controlled trial (RCT)
2. to evaluate the clinical role of CGMs, in terms of efficacy, safety, utility and cost-effectiveness, through a multicentre RCT
3. to pilot the potential use of a closed-loop system for glucose control using CGMs.

Chapter 2 Feasibility study

Aim

The aim of the study was to carry out preliminary evaluation of feasibility of real-time CGM to inform the design of a larger RCT in the preterm population.

Objectives

The objectives of the feasibility study were to determine provisional data regarding:

- recruitment potential for a RCT
- accuracy and safety of the devices for use in the preterm population
- user acceptability, including the impact on clinical care and frequency of blood glucose testing
- prevalence of the anticipated primary outcome measure (i.e. time in glucose target range of 2.6–10 mmol/l).

Methods

Study design

This was a single-centre study, with infants recruited from the NICU at Addenbrooke's Hospital, Cambridge, UK. Ethics and trust research and development approval were obtained prior to the start of study recruitment, and informed parental consent was obtained prior to any study procedures. Inclusion criteria were infants with a birthweight ≤ 1200 g and aged ≤ 48 hours for whom informed parental consent had been received. Infants were excluded if they had a major congenital malformation or an underlying metabolic disorder, or if the mothers had a pregnancy complicated with diabetes. The intervention lasted for up to 7 days. Data regarding glucose levels, clinical condition and nutritional intake, as well as insulin use, were collected prospectively.

Continuous glucose monitoring and management

Real-time CGM was performed using the Paradigm® Veo™ system (Medtronic plc) (*Figure 1*). Enlite™ sensors (Medtronic plc) were linked to the Paradigm® Veo™. The sensor glucose data could be viewed in real time and were used in conjunction with the guideline to support clinical management. The guideline provided simple guidance, was not a rigid guideline and had not undergone formal in silico testing. The nurses recorded the sensory glucose value, alongside standard hourly clinical observation, using it to guide the need for blood glucose testing. The guideline prompted review and intervention based on both absolute glucose levels and change. The CGM devices were calibrated at least twice daily using a blood glucose measured on the point-of-care (POC) StatStrip® meter (Nova Biomedical, Waltham, MA, USA). The StatStrip meter was chosen because it has been validated for accuracy in the newborn and intensive care settings.

Blood glucose monitoring

Blood glucose levels were measured using a combination of arterial, venous and capillary samples, and were tested on the blood gas analyser (cobas b 221; Roche Diagnostics, Welwyn Garden City, UK) and the Nova StatStrip.
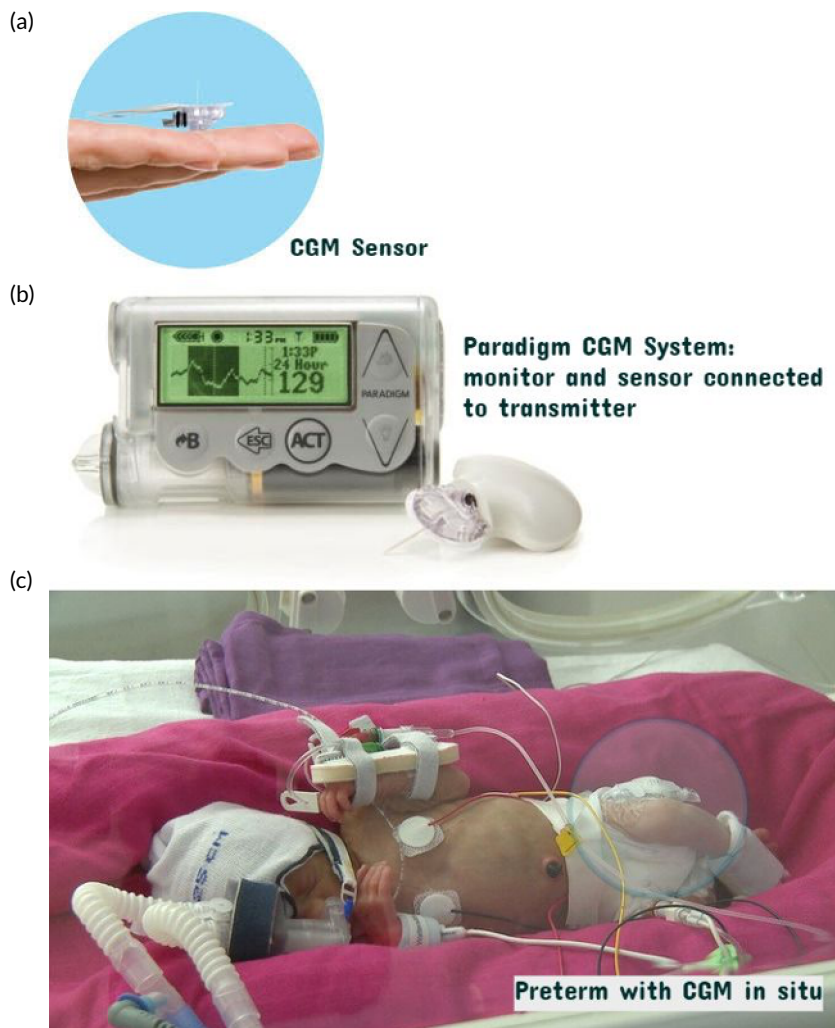
FIGURE 1 Continuous glucose monitoring system. (a) Enlite sensor; (b) Paradigm Veo and MiniLink® REAL-Time Transmitter (Medtronic plc) attached to a sensor; and (c) preterm infant with device in situ. Reproduced with permission from Thomson *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Analyses

Accuracy of the continuous glucose monitor

Prespecified comparative analyses were based on any glucose levels that were recorded within 5 minutes of each other. The median relative difference was calculated as the percentage difference between the two measures. Absolute differences were determined at each time point in terms of compliance with International Organization for Standardization (ISO) 2003 and 2013 standards.[31,32] Bland–Altman analysis was used for assessment of error between glucose measurements and error grid plots were used to explore potential clinical impact.

Safety of the continuous glucose monitor

Safety outcomes were defined as prevalence of hypoglycaemia (percentage of time with sensor glucose level < 2.6 mmol/l) and any single blood glucose reading of < 2.6 mmol/l, and/or more than six sensor glucose readings of < 2.6 mmol/l (i.e. > 30 minutes).

Utility

The clinical care team were invited to complete a comments sheet daily for immediate feedback, as well as an anonymised questionnaire for summative review. The questionnaires explored initial expectations and experiences of using the CGM. These questionnaires were developed in collaboration with nurses on the unit to ensure that questions were easy to understand and relevant to the individuals concerned.

Efficacy outcome

Predefined efficacy outcomes included time in target range (i.e. percentage of time with a sensor glucose level 2.6–10 mmol/l or 4–8 mmol/l), prevalence of hyperglycaemia (i.e. percentage of time with a sensor glucose level > 10 mmol/l) and prevalence of severe hyperglycaemia (i.e. percentage of time with a sensor glucose level > 15 mmol/l).

Results are expressed as mean [standard deviation (SD)], median [interquartile range (IQR)] or frequencies (percentages), as appropriate.

Results

Recruitment

Twenty-one infants were successfully recruited to the feasibility study. One infant was withdrawn because of failure of sensor insertion. The baseline demographic details of the remaining 20 infants with CGM data are shown in *Table 1*. The recruitment rate fluctuated widely from month to month and was delayed by two factors: (1) availability of eligible infants to approach and (2) availability of appropriately trained staff to undertake the study procedures. During the recruitment period, the NICU underwent a period of reduced admissions associated with the introduction of a new electronic medical records system, resulting in fewer infants being admitted and available for recruitment. In addition, sensor insertion was initially limited to key study staff to facilitate a core of experience within the team. However, the unpredictability of preterm deliveries, combined with the need for many mothers to be transferred from other hospitals, resulted in a very small window for recruitment and meant that staff with the key skills for sensor insertion were not always available.

TABLE 1 Feasibility study: baseline demographic data

Baseline demographic data	Feasibility study (N = 20)
Gestational age at birth (weeks), mean (SD)	26.14 (1.9)
Birthweight (g), mean (SD)	809 (156)
Sex (male-to-female)	10 : 10
Antenatal variable, *n* (%)	
Antenatal steroids	19 (95)
Maternal smoking	5 (25)
Chorioamnionitis	1 (5)
PROM	6 (30)
Hypertension	1 (5)

PROM, prelabour rupture of membranes.

Accuracy of continuous glucose monitors

Comparative data providing more than two glucose measurements (blood glucose or sensor glucose) taken within 5 minutes of each other were available at 247 time points. Bland–Altman analyses provided a mean bias between POC and CGM of –0.27 [95% confidence interval (CI) –0.35 to –0.19] (*Figure 2*). Error grid analyses (comparing sensor glucose with either blood glucose methodology) demonstrated that 98% of values lay within area A or B (see *Figure 2*). Performance in relation to the ISO 2003[31] and ISO 2013[32] standards is provided in *Table 2*.

FIGURE 2 Feasibility study: Bland–Altman and error grid plots.[33] (a) Bland–Altman comparison of CGM sensor glucose with StatStrip meter; (b) error grid plot comparing CGM sensor glucose with StatStrip meter or blood gas (cobas b 221) glucose values; (c) Bland–Altman comparison of POC StatStrip meter with blood gas (cobas b 221) glucose values; (d) error grid plot comparing POC StatStrip meter with blood gas (cobas b 221) glucose values; (e) Bland–Altman comparison of CGM sensor glucose with blood gas (cobas b 221) glucose values; and (f) error grid plot comparing CGM sensor glucose with blood gas (cobas b 221) glucose values. BG, blood glucose; SG, sensor glucose. Orange dots represent outliers whose results were reviewed and were deemed to be secondary to pre-analytical error in blood glucose sampling. The reference lines show the estimate of the mean difference, 95% CIs around the mean estimate and the predictive interval, the region in which a new observation would be expected, with 95% confidence, to be observed. Reproduced with permission from Thomson *et al.*[1] This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

(c)

Bland–Altman comparing BG and POC
(BG, POC and SG within 5 minutes)

(d)

Error grid analysis comparing BG and POC
(BG, POC and SG within 5 minutes)

FIGURE 2 Feasibility study: Bland–Altman and error grid plots.[33] (a) Bland–Altman comparison of CGM sensor glucose with StatStrip meter; (b) error grid plot comparing CGM sensor glucose with StatStrip meter or blood gas (cobas b 221) glucose values; (c) Bland–Altman comparison of POC StatStrip meter with blood gas (cobas b 221) glucose values; (d) error grid plot comparing POC StatStrip meter with blood gas (cobas b 221) glucose values; (e) Bland–Altman comparison of CGM sensor glucose with blood gas (cobas b 221) glucose values; and (f) error grid plot comparing CGM sensor glucose with blood gas (cobas b 221) glucose values. BG, blood glucose; SG, sensor glucose. Orange dots represent outliers whose results were reviewed and were deemed to be secondary to pre-analytical error in blood glucose sampling. The reference lines show the estimate of the mean difference, 95% CIs around the mean estimate and the predictive interval, the region in which a new observation would be expected, with 95% confidence, to be observed. Reproduced with permission from Thomson *et al.*[1] This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

(e)

Bland–Altman comparing BG and SG
(BG, POC and SG within 5 minutes)

(f)

Error grid analysis comparing BG and SG
(BG, POC and SG within 5 minutes)

FIGURE 2 Feasibility study: Bland–Altman and error grid plots.[33] (a) Bland–Altman comparison of CGM sensor glucose with StatStrip meter; (b) error grid plot comparing CGM sensor glucose with StatStrip meter or blood gas (cobas b 221) glucose values; (c) Bland–Altman comparison of POC StatStrip meter with blood gas (cobas b 221) glucose values; (d) error grid plot comparing POC StatStrip meter with blood gas (cobas b 221) glucose values; (e) Bland–Altman comparison of CGM sensor glucose with blood gas (cobas b 221) glucose values; and (f) error grid plot comparing CGM sensor glucose with blood gas (cobas b 221) glucose values. BG, blood glucose; SG, sensor glucose. Orange dots represent outliers whose results were reviewed and were deemed to be secondary to pre-analytical error in blood glucose sampling. The reference lines show the estimate of the mean difference, 95% CIs around the mean estimate and the predictive interval, the region in which a new observation would be expected, with 95% confidence, to be observed. Reproduced with permission from Thomson et al.[1] This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 2 Feasibility study: comparison of sensor glucose measurements with POC glucose values

Standard	Criterion	Blood glucose (%)	POC (%)
MARD	Per cent difference between sensor glucose and reference (sensor glucose – reference)/reference × 100	11	10
ISO 2003[31]	Per cent of sensor glucose values within ± 20% of the blood glucose value	84	90
ISO 2013[32]	Per cent of sensor glucose values within ± 0.83 mmol/l of blood glucose value	73	78

MARD, mean absolute relative difference.

Notes
System accuracy standards of 2003 (ISO 15197:2003)[31] state that 95% of blood glucose results should be within ± 0.83 mmol/l of laboratory results at concentrations of < 4.2 mmol/l, or within ± 20% of laboratory results at concentrations of > 4.2 mmol/l. System accuracy standards 2013 (ISO 15197:2013)[32] require 95% of blood glucose results to be within ± 0.83 mmol/l of laboratory results at concentrations of < 5.6 mmol/l, or within ± 20% of laboratory results at concentrations of > 5.6 mmol/l.

Safety

There were no serious adverse device effects (SADEs). One infant died prior to discharge from hospital, but after the intervention period. Death was due to prematurity and felt to be unrelated to the study intervention. One infant was withdrawn from the study early as the mother became acutely unwell and, in the light of the mother's mental health, it was felt appropriate to withdraw the infant from the study. One infant was withdrawn because of failure of sensor insertion. This was the second infant recruited to the study. The Enlite sensor failed to insert on two attempts and remained within the needle guard. There were no concerns about infection or trauma at the site of sensor insertion and the CGM device did not interfere with clinical care.

There were three infants who had clinically documented episodes of hypoglycaemia, defined as any blood glucose measurement < 2.6 mmol/l. In each of these infants, the falling sensor glucose level had prompted action to be taken to check the blood glucose level. There were no concerns about the infants during these episodes and without the falling sensor glucose level the blood glucose level would not have been checked. After confirming a blood glucose level < 2.6 mmol/l, these infants were treated with intravenous dextrose. In two cases, the falling sensor glucose level also revealed failure of central access. In two of these episodes, sensor glucose values were also < 2.6 mmol/l (recorded on the CGM devices as episodes lasting 40 and 25 minutes, respectively). In the other case, the lowest sensor glucose value was 2.7 mmol/l. There was one further episode when the sensor glucose fell to < 2.6 mmol/l for 70 minutes, but this was not documented clinically because of a protocol deviation, as blood glucose was not measured at this time. There were no concerns about any of the infants during any of these episodes and the infants were not receiving any insulin.

Utility

The overall assessment of the CGM devices by research and clinical staff was that they were easy to use in terms of insertion and calibration. There were occasions when there was loss of connectivity between the sensor and the monitor (e.g. if an infant was moved out of an incubator for kangaroo care or someone stood between the infant and the monitor). On such occasions, it was evident that the transmitter range was limited if transmission was blocked by objects between the sensor and the monitor. This could be resolved by moving the monitor closer to the infant. Staff found the use of both predictive and threshold alarms challenging, considering them an unnecessary addition to recording sensor glucose levels hourly. As a result of frequent requests to silence these alarms, they were subsequently turned off in the early stages of the study to ensure continued staff engagement.

With a need for twice-daily calibrations, the median number of blood samples taken for glucose measurement per 24-hour period did not appear to be excessive or significantly different from the number of samples taken in other infants of similar gestational and postnatal age on the unit. The median of the mean number of samples per day per infant was 4.1 (range 3.3–4.3).

Staff expectations varied greatly, with some nurses excited about the potential to limit the need for frequent blood glucose sampling and avoiding 'hurting the baby'; however, others had concerns about increased workload, sensor insertion, risk of 'tissue damage' or difficulties in positioning an infant following sensor insertion. Comments varied from 'exciting' to 'how much extra time will it take up?'. After caring for an infant using CGM, there was an over-riding view that the intervention improved the quality of care (*Figure 3*). Comments included 'found the monitor to be useful when the infant was on insulin', 'the chart … is really useful', 'I think this is the best treatment' and 'it is not extra workload'. Nursing staff reported positively about the impact on care in terms of feeling more empowered to manage the infant's glucose control. They did not report any significant negative effects for the infant or the clinical/nursing team caring for the infant.

FIGURE 3 Feasibility study: staff assessment of the use of continuous glucose monitoring.[1] (a) Do you think the baby is distressed?; (b) How did you find the monitor to read and calibrate?; (c) Do you think the device has interfered with the nursing care?; (d) Did having the baby on the monitor significantly affect your workload?; and (e) Did you think that being able to monitor glucose continuously had an impact on clinical care? Data are presented as a per cent of the responses received. Reproduced with permission from Thomson *et al.*[1] This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure. (*continued*)

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Efficacy

A total of 2626 hours of CGM data were collected from 20 infants, with a median for individual infants of 144 (range 7–166) hours. There was wide variability in glucose control in this population. Data demonstrating the percentage of time within different target thresholds are provided in *Table 3*. The median percentage of time in the target range of 2.6–10 mmol/l was 78% (IQR 59–94%), with values > 10 mmol/l recorded 22% of the time.

Discussion

This study was the first to explore the potential role of 'real-time' CGM to support targeting of glucose control, with guidance on insulin and glucose delivery in preterm infants. The feasibility study highlighted the challenges of recruiting to a complex interventional study when recruitment has to occur at unpredictable times and within a very short time frame. The devices were found to be sufficiently accurate to guide clinical management and the sensors were well tolerated, despite the infants' low birthweight, limited subcutaneous tissue and potential risk of infection. Furthermore, the staff felt that the intervention led to improved care.

Recruitment within the feasibility study was noted to be onerous to the research team. This was related to the unpredictability of infants being delivered, combined with the tight time frame. The feasibility study also showed that the burden of recruitment, combined with a complex intervention, was likely to present considerable challenges to the delivery of a multicentre trial. In most units, key staff are usually trained to undertake consent for trials, but interventions such as a change in feeding practice or even investigational medicinal product delivery can be undertaken by core clinical staff. As a device study, identifying the key skill sets needed to undertake the study and the optimal number of staff needed to support recruitment was seen as critical. There was a need for staff with the key skills

TABLE 3 Feasibility study: efficacy outcomes relating to glucose control

Outcome	Value (*n* = 20)
Percentage of time sensor glucose in range	
2.6–10.0 mmol/l[a]	78 (59–94)
4.0–8.0 mmol/l	46 (35–66)
> 10.0 mmol/l	22 (6–41)
< 2.6 mmol/l	0 (0–0)
Mean sensor glucose (mmol/l)	8.3 (7.4–9.4)
SD of sensor glucose (mmol/l)	2.39 (1.77–3.67)
Hypoglycaemia (sensor data)	
Number of infants with more than one episode of hypoglycaemia	2
Number of episodes of hypoglycaemia	2
Total length of episodes (minutes)	40–70
Blood glucose (< 2.6 mmol/l)	
Number of episodes of hypoglycaemia	3[b]

a Primary end point.
b A hypoglycaemic episode was defined as any blood glucose measurement of < 2.6 mmol/l or sensor glucose measurement of < 2.6 mmol/l for > 30 minutes. There was one recording of blood glucose < 2.6 mmol/l, but the sensor glucose level fell to a nadir of only 2.7 mmol/l.

Note
Data are presented as median (IQR).

for sensor insertion and who were able to guide the clinical team regarding the protocol to be available 24 hours a day, 7 days a week, for optimal recruitment. This informed the development of training packages for unit staff, including a video guide to sensor insertion and packages of example cases for the use of the guideline for glucose control and further informed the plans for the subsequent RCT.

The data showed the CGM devices to be of comparable accuracy to the POC devices that are currently used in clinical practice. The median absolute relative difference was similar to that reported in other paediatric and intensive care studies.[34,35] There were episodes when only one of sensor glucose or blood glucose level reached the threshold for hypoglycaemia, but the trend in falling sensor glucose level had prompted the measurement of blood glucose. The blood glucose level would not have been checked if the sensor had not triggered a clinical concern and the episode of hypoglycaemia would have been clinically undetected. Differences may, in part, be related to the physiological differences between blood and interstitial glucose levels, particularly with rapidly changing blood glucose levels.[36]

There was no increase in risk of hypoglycaemia with a more proactive approach to management of hyperglycaemia, that is when using the guideline alongside the real-time monitoring. This is in contrast to previous attempts to target glucose control with insulin in adult or neonatal intensive care, which have resulted in significant increases in the prevalence of hypoglycaemia.[15] In this study, use of CGM devices provided an opportunity to track changes in glucose control in real time. This was important in providing guidance to clinical staff about glucose management in a population, that is infants in the NICU, in whom drug infusions (both types of drugs and dosing), as well as insulin sensitivity and secretion, change both frequently and rapidly, leading to a risk of hypoglycaemia. This was highlighted by the fact that two infants experienced hypoglycaemic episodes (related to loss of central access) that first became apparent because of the falling sensor glucose value.

The aim was not for CGM to replace blood glucose sampling, but to augment it, and the number of blood glucose samples taken in these infants was comparable to the number of samples taken from other infants of a similar gestational and postnatal age within the unit. This is in keeping with the advice given to the clinical nurses during the study, which was to check blood glucose values before modifying any aspect of the management of glucose control. For example, changes in insulin dosing were undertaken only in response to a persistent rising glucose level on the CGM device and supported by a confirmatory blood glucose measurement. During the study, however, nursing staff became more confident in the accuracy of the sensor glucose values and, with the guideline, they began to change dosing based on sensor glucose values alone. They began to use blood glucose values in a more proactive way to confirm observed trends in the CGM. Increasing confidence in the accuracy of CGM devices and the desire to limit handling of preterm infants may lead to reduced blood glucose sampling in the future.

One infant (the second infant recruited) was withdrawn from the study because of failure on two occasions to successfully place a sensor. For this infant, on both occasions, the sensor remained within the needle guard and did not insert into the thigh. This event had been previously reported in paediatric and adult patients, but had not been experienced by the research team with previous Softsense sensors (Medtronic plc). On reviewing the potential causes, the advice on insertion technique was modified to focus on ensuring that the needle and sensor remained at 90° to the hub until after the introducer needle was removed. There were no further occurrences during the feasibility study. The sensor appeared to be safe, with no reports of infection or debridement of skin at the sensor site in this preterm population.

The lack of benefit from predictive trend alarms was disappointing, but it may be that with more experience the alarms could be used. However, the system was reported by the nursing staff to be beneficial to clinical care. The clinical team reported feeling that the combination of the CGM device and guideline was useful in caring for the infant.

We chose a strategy that aimed to optimise nutritional intake, using the intervention to inform decisions on insulin and glucose therapy in the event of hyperglycaemia or hypoglycaemia. Other strategies can also be used to target glucose control in preterm infants, each with different risks and benefits. One such alternative strategy, that of reducing parenteral intake, risks compromised nutritional delivery, as found in a recent study in preterm infants using CGM and a computer algorithm to modify glucose intake in response to hyperglycaemia.[37] Our study is unique in combining the use of a CGM with a guideline for the use of insulin and glucose therapy. This design is easy to adopt in clinical practice as it does not involve the need for frequent changes to parenteral nutrition, which may affect nutritional and electrolyte delivery, as well as staff workload and cost. Moreover, we have shown in this feasibility study that this strategy does not increase the risk of hypoglycaemia.

The efficacy outcome of percentage of time with glucose level in the target range (i.e. 2.6–10 mmol/l) was reviewed by the trial statistician to inform power calculations for the planned multicentre RCT of real-time CGM compared with standard care. The data were used to confirm sample size considerations based on a final analysis comparing the percentage of time in the target range (2.6–10 mmol/l), that is a continuous variable, in terms of the mean values between the treatment arms. Based on these data, the SD of this end point was conservatively estimated at 22%; hence, a sample size of 200 infants would provide 90% power to detect a difference of 10% at the 5% significance level. Consensus was reached among expert opinion at the Trial Steering Committee (TSC) and Data Monitoring Ethics Committee (DMEC) meetings that a 10% difference would be clinically meaningful. The comparison between the mean values in *Table 3* provides support to an effect size of 10%, or more being plausible.

Summary

The feasibility study confirmed reasonable accuracy and utility of the combination of CGM plus the guideline for blood glucose testing and subsequent intervention within a clinical trial. It further informed the need to innovate to maximise recruitment potential and staff engagement, while providing data to substantiate the power calculations for the primary outcomes within such a trial.

Chapter 3 REACT trial design

Introduction

Data from the feasibility study helped to design this RCT. Those involved in recruitment pointed out that the short time period from birth to study entry was a challenge and, therefore, an online training video was developed to enable training of a larger number of staff in recruiting sites to support recruitment and delivery of the intervention. There were no safety flags in terms of the CGM device itself. In the context of using CGM as an adjunct to current methods of blood glucose monitoring, CGM was confirmed to be sufficiently accurate to safely support glucose management. Provisional data on the combination of the CGM and guideline to guide targeting of glucose control did not give rise to any safety concerns in terms of risks of hypoglycaemia. Data on the prevalence of the anticipated primary outcome measure of time in glucose target range (i.e. 2.6–10 mmol/l) confirmed an estimated SD of 22%, which was in keeping with the planned sample size of 200 infants. Furthermore, the staff questionnaire demonstrated that the clinical team caring for infants felt that CGM has the potential to improve clinical care.

Aim

To evaluate the clinical role of CGM in the preterm infant, in terms of efficacy, safety, utility and cost-effectiveness, through a multicentre RCT.

Hypothesis

We hypothesised that the use of real-time CGM could increase the amount of time that an infant's glucose levels (measured using CGM) are within the target range of 2.6–10 mmol/l (i.e. the widely accepted clinical target for glucose control) compared with standard clinical practice (with blinded CGM data collection).

Trial objectives

The primary efficacy outcome was percentage of time for which glucose levels were within the glucose target range of 2.6–10 mmol/l over 6 days, following recruitment within 24 hours of birth.

Secondary outcomes related to:

- efficacy (i.e. mean sensor glucose level, percentage of time sensor glucose levels are in the target range of 4–8 mmol/l, sensor glucose level variability, percentage of time sensor glucose levels are > 15 mmol/l)
- safety, as measured by both device effects and incidence of hypoglycaemia
- utility assessed by staff and parent questionnaires
- cost-effectiveness
- exploratory analyses.

Methods

Study design

This study was an international open-label parallel-group RCT, with infants recruited between July 2016 and January 2019 from 13 NICUs in the UK, Spain and the Netherlands. The protocol has been published.[2]

Eligibility criteria

Infants were eligible if they were within 24 hours of birth, weighed $\leq$ 1200 g and were born at $\leq$ 36[+6] weeks gestation, and if written parental consent had been obtained. Exclusion criteria included any lethal congenital malformations and any congenital metabolic disorder known at trial entry. Infants were also ineligible if, in the opinion of the treating clinical consultant, they had no realistic prospect of survival.

Recruitment procedure

All infants were recruited within 24 hours of birth at one of the NICUs that had been approved for study participation as a level 3 unit with capacity and capability to recruit. Owing to the short time frame from birth to recruitment, potentially eligible infants were identified in a number of ways: (1) liaison with the obstetric team to highlight mothers at risk of preterm delivery, (2) liaison with the neonatal transport team to identify infants who had been born in local units and being transferred to a study centre and (3) liaison with the NICU clinical team of study centres. Screening of eligible infants was undertaken in collaboration with the clinical team and families were approached for consent only if they were considered eligible. Screening logs were reviewed regularly by the co-ordinating centre to identify any issues around recruitment. The investigator or a suitably qualified person designated by the principal investigator was able to receive written informed consent from the infant's parent/legally acceptable representative before any trial-specific activity was performed.

Randomisation and blinding

Randomisation to the standard-care and CGM arms of the study in a 1 : 1 ratio was undertaken centrally using a web randomisation system, Trans European Network ALEA software (TENALEA; ALEA Clinical, Abcoude, The Netherlands). This used block randomisation, with blocks of random size (i.e. 4, 6, 8) stratifying by recruiting centre and gestation (< 26 or $\geq$ 26 weeks' gestation). The management of glucose control and use of CGM from recruitment at aged $\leq$ 24 hours until day 7 were predetermined in the protocol for each study arm.[2] Clinical outcome data were collected until 36 weeks' corrected gestational age. No other aspects of concomitant care were prohibited during the trial.

Intervention

All infants were fitted with a sensor (i.e. the Enlite glucose sensor) that was linked to a MiniMed™ 640G System (Medtronic plc). Sensors were inserted subcutaneously (into the thigh) by hand and not using the standard insertion device, thereby ensuring that the sensor was inserted into the subcutaneous tissue. The sensors are soft and flexible, approximately 8.75 mm in length, and are mounted inside a hollow needle to allow for subcutaneous insertion. Once the sensor was inserted, the introducer needle was withdrawn and the sensor attached to a small Guardian™ 2 Link transmitter [Medtronic plc; Conformité Européenne (CE) Mark 2013; certificate number 8858] for data transfer to the MiniMed 640G System for data viewing. The sensors were secured with a clear occlusive dressing so that the insertion site could be inspected daily. A blood sample was required every 12 hours for calibration. For consistency across sites, all units were provided with Nova StatStrip meters for calibration of the CGM.

Intervention: real-time continuous glucose monitoring with guideline

The CGM data were available to view by the clinical team during the first week of life. Clinical staff were advised to read and record the sensor glucose data hourly as part of standard clinical care.

They were provided with a specifically designed guideline to guide the management of glucose control and the use of insulin. The guideline was developed during the REACT feasibility study.[1]

Control: standard care with blinded continuous glucose monitor data collection

Blinding of the study intervention between study groups was not feasible. To ensure that CGM data were not available to the clinical team caring for infants in the standard-care arm, the monitors were secured in an opaque bag with a tamper-proof seal. The bags were opened for calibration every 12 hours and a time log was kept of when the tamper tag was broken/resealed to document compliance.

Infants' glucose control was monitored and managed in accordance with standard clinical practice based on intermittently sampled blood glucose levels. Nutritional requirement and insulin delivery were prescribed in accordance with standard clinical guidelines within each unit. The CGM device collected glucose data continuously, but the clinical team were masked to the data, as described above.

Medical devices: MiniMed 640G System

The MiniMed 640G System is indicated for glucose monitoring for the management of diabetes (*Figure 4*). The system being used comprised the Enlite sensor linked using the Guardian™ 2 Link transmitter to the MiniMed 640G. The Enlite sensor (CE certificate number 21024) has been described previously and comprises a disposable subcutaneous oxidase-based platinum electrode that catalyses interstitial glucose, generating an electrical current every 10 seconds that is transmitted to a monitor. The data were recorded as an averaged value every 5 minutes, giving a total of 288 readings per day. Glucose values outside the range of 2.2–24 mmol/l (40–430 mg/dl) are reported as < 2.2 mmol/l (40 mg/dl) or > 24 mmol/l (430 mg/dl).

Data management and schedule of assessments

Data collection was undertaken from birth to 36 weeks' corrected gestational age, and comprised the collection of clinical data recorded on a paper case report form (CRF) and electronic transfer of CGM data. Key time points for clinical data collection were recruitment, daily for the first week, day 14 followed by end of study at 36 weeks' corrected gestational age and, if appropriate, at the point of withdrawal from the study. Parent and staff questionnaires were completed in the CGM group at study days 3 and 7. CGM data were transferred electronically after download from the CGM device on study day 7 or the day of sensor removal. Safety data were collected and reported in accordance with regulatory guidance. If an infant was discharged from their recruiting NICU, the research team used local and national databases, local contacts and links with parents to ensure that complete follow-up data were obtained. All CRF data were sent to the co-ordinating centre in Cambridge to be entered onto a macro-database. All CGM files were sent to the co-ordinating centre in Cambridge for validation on format and consistency before processing and analysis. All data were collected, transferred (using a study identifier), cleaned and stored to comply with good clinical practice and data protection legislation.

Efficacy
Efficacy was assessed by comparing the data collected from the CGM in the CGM and standard-care arms of the study.

Safety
Safety was assessed in three areas: (1) incidence of hypoglycaemia, measured as part of clinical care (blood glucose levels) and after review of sensor glucose data; (2) device safety through adverse device effect (ADE) reporting; and (3) acute mortality and morbidity outcomes as part of the CRF.
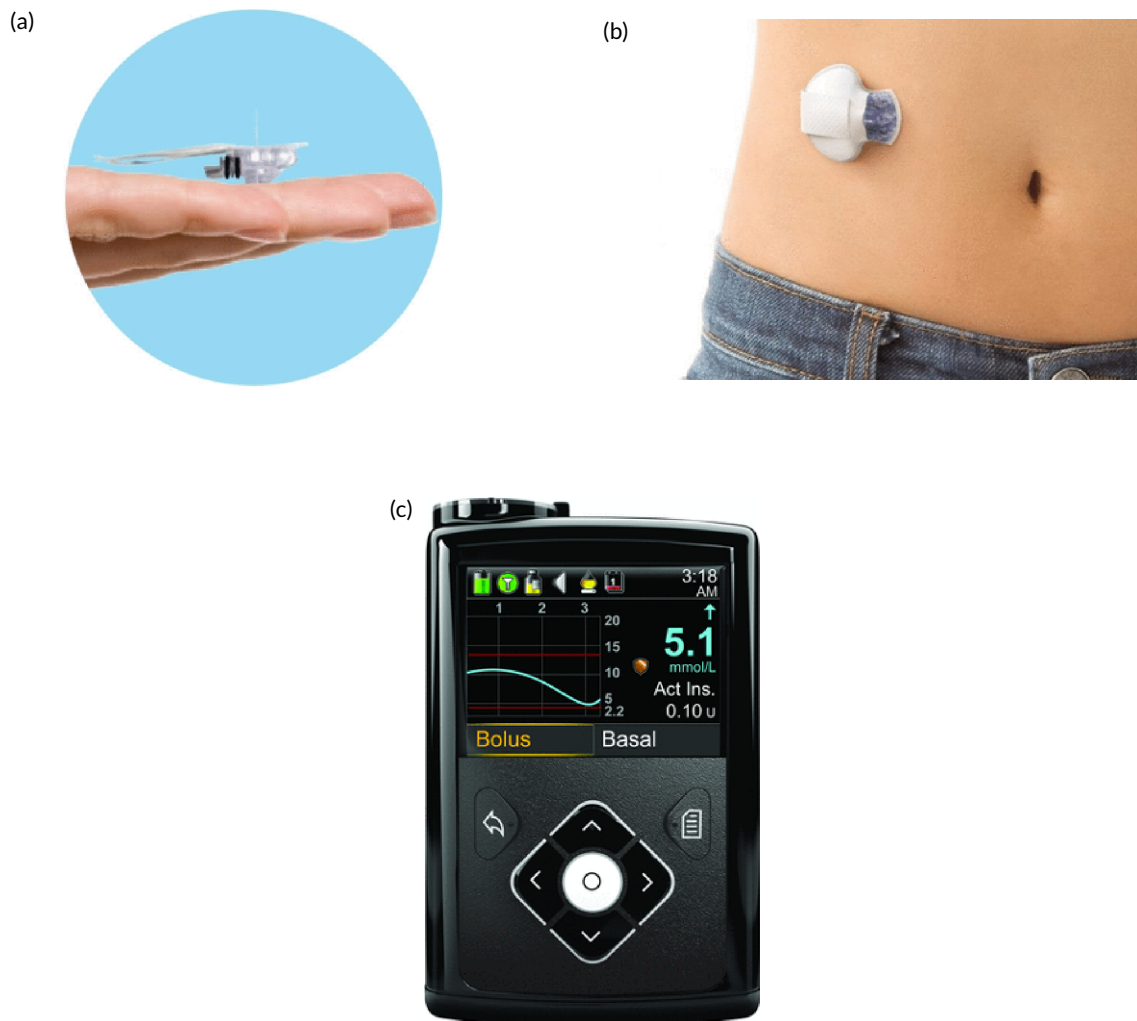
FIGURE 4 The MiniMed 640G System (courtesy of Medtronic plc). (a) The Enlite glucose sensor; (b) the Enlite glucose sensor with the Guardian 2 Link transmitter attached; and (c) the MiniMed 640G.

Utility

Nursing staff and parents caring for the infants in the CGM arm of the study were asked to complete a study-specific questionnaire.

Health economic evaluation

Data were collected on the health service resources used in the treatment of infants during the period between randomisation and 36 weeks' gestational age, and based on the British Association of Perinatal Medicine standard criteria for level of care,[38] as well as neonatal complications. Current UK unit costs were applied to each resource item and a per diem cost for each level of neonatal care was based on Department of Health and Social Care reference costs calculated on a full absorption costing basis.[39]

Outcomes

Primary outcome

The primary outcome was defined as the percentage of time that the sensor glucose level was in the target range of 2.6–10 mmol/l. This was selected as the internationally most widely accepted clinical target range for glucose control in this population.

Secondary outcomes

Efficacy

- Percentage of time sensor glucose level is in the target range of 4–8 mmol/l.
- Mean sensor glucose level during the first 6 days.
- Sensor glucose level variability within infants (as assessed by within-infant SD).
- Percentage of time that glucose levels are in hyperglycaemic range (i.e. a sensor glucose level > 15 mmol/l).

Safety

- Incidence of moderate hypoglycaemia, defined as any episode of blood glucose > 2.2 mmol/l and < 2.6 mmol/l.
- Incidence of severe hypoglycaemia, defined as any episode of blood glucose ≤ 2.2 mmol/l.
- Incidence of continuous hypoglycaemia, defined as a continuous episode of sensor glucose level < 2.6 mmol/l for > 1 hour.

Utility

- The questionnaire comprised key questions that were scored using a Likert scale.

Health economic outcomes

Cost-effectiveness was expressed in terms of incremental cost per additional case of adequate glucose control between 2.6 and 10 mmol/l.

Exploratory outcomes

Exploratory outcomes included mortality before 36 weeks' corrected gestational age, maximum severity of ROP, bronchopulmonary dysplasia (BPD) (i.e. the need for supplemental oxygen or respiratory support at 36 weeks' corrected gestational age), microbiologically confirmed or clinically suspected late-onset invasive infection, necrotising enterocolitis (NEC), patent ductus arteriosus (PDA) requiring medical or surgical treatment, maximum grade of intracranial haemorrhage (Papile and Burstein grading), growth (weight, length and head circumference at the end of week 1 and at 36 weeks' corrected gestational age), nutritional intake during the first week of life (carbohydrate, protein and lipid), and use of insulin during the first and second week of life.

Sample size

The sample size was based on data from the REACT feasibility study and historical control data, which conservatively assumed that the SD of the primary end point (i.e. time in sensor glucose target range of 2.6–10 mmol/l over a 6-day period) would be 22%. A sample size of 200 participants would enable a treatment effect of a 10% increase in the mean value of the primary end point to be detected with 90% power using a two-sided 5% significance test in the primary analysis. Based on a consensus of expert opinion, a difference of 10% was believed to be of clinical relevance. It was expected that a small number of infants would be withdrawn from the study because of transfer to local units, withdrawal of parental consent or death.

At an interim analysis, a revised blinded estimate of the SD for the primary end point suggested that the original sample size would provide 92.5% power. After review of recruitment rates and undertaking a revised power calculation using the revised blinded estimate of the SD for the primary end point, a decision was made by the independent DMEC, TSC and sponsor to stop recruitment when 182 infants had been recruited. At this time, it was considered that concluding the study with

182 infants rather than the planned 200 would reduce the conservative estimate of power from 92.5% to 90%, which was felt to be an acceptable compromise to be able to report trial results within the desired timelines.

Statistical analyses

Efficacy analyses

Analyses were predetermined to be undertaken based on 'full analysis' (primary outcome) and 'per-protocol' populations to compare the CGM group with the standard-care group and were prespecified in the statistical analysis plan. Linear regression was used to estimate the absolute difference in the percentage of time that the sensor glucose level was in the target range of 2.6–10 mmol/l, adjusting for baseline variables (i.e. centre and gestation). Estimates of treatment effect, with 95% CIs and p-values, were calculated. Secondary end points that were continuous variables were analysed in a similar fashion and binary/ordinal variables were analysed using logistic/ordinal logistic regression.

To control the study-wide significance level to 5%, a Benjamini–Hochberg multiple testing procedure was applied to three end points of equal importance (i.e. the percentage of time that the sensor glucose level was in the target range of 2.6–10 mmol/l, the percentage of time that the sensor glucose level was in the target range of 4–8 mmol/l and mean sensor glucose level), followed by a gatekeeping sequence applied in the following order: sensor glucose variability, as assessed by within-infant SD; and percentage of time that glucose levels were in the hyperglycaemic range (i.e. sensor glucose level > 15 mmol/l). Nominal p-values and CIs are presented, unless otherwise stated.

Predefined subgroup analyses were undertaken by estimating, using the regression framework in an exploratory, non-confirmatory manner, treatment interaction effects with the following baseline variables: centre, sex, corrected gestational age, birthweight standard deviation score (SDS), use of antenatal steroids, maternal chorioamnionitis, maternal diabetes and first sensor glucose level.

Utility analyses

Acceptability of the intervention was assessed by a specifically designed staff questionnaire, which was completed anonymously by staff caring for an infant in the CGM arm on days 3 and 7, and by a similar parent questionnaire (completed on day 7). Compliance in the CGM group was assessed as a percentage of time that sensor glucose readings were recorded on the CRF and when the insulin rate of infusion was recorded if the sensor glucose > 8 mmol/l. In the standard-care group, non-compliance was defined as 12 or more CGM readings available during the time between the tamper tag being broken and resealed on at least one occasion.

Cost-effectiveness analyses

An incremental cost-effectiveness analysis was performed, details of which are presented in *Chapter 5*.

Study management

The study was co-ordinated and monitored by the Cambridge Clinical Trials Unit (Cambridge, UK) in accordance with international guidelines. The study was adopted onto the National Institute for Health Research Clinical Research Network portfolio of studies.

Regulatory requirements

Ethics and regulatory approvals were obtained and the protocol is in the public domain (ISRCTN12793535),[2] with a list of protocol amendments provided in *Appendix 1*. A DMEC and TSC were appointed and reviewed the data in accordance with their formal charters (see *Appendices 2* and *3*). Research teams at each site were required to have up-to-date good clinical practice training and have undertaken

training in study procedures, including the use of the CGMs and Nova Biomedical POC devices. Paper and online resources, as well as a call line, were available to support the research teams.

Clinical trial authorisation was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) (reference CI/2016/0011). Written approvals were received from individual hospital sites prior to recruitment. Approvals were also obtained from the Medical Ethics Review Committee (Vrije Universiteit University Medical Centre, Amsterdam, the Netherlands) and Heath Care Inspectorate (Heerlen, the Netherlands) (reference 2017-1 398434/VIO 14949), the Research Ethics Committee, Sant Joan de Déu Research Foundation (Barcelona, Spain), and the Ministry of Health Social Services and Equality (reference 591/16/EC) (Madrid, Spain). The trial was conducted in accordance with the principles of the Declaration of Helsinki[40] and in conformity with the European Union medical devices regulations and any relevant amendments.[41]

Monitoring

Data returns were continually monitored by the central team for the completeness and timeliness of all data returned. Compliance with intervention strategy in each study arm was also reviewed to ensure that there was no 'crossover' between study arms. A monitoring plan was in place, determining frequency and scope of site monitoring based on continuing risk review. Face-to-face monitoring visits were initially undertaken within the first 6 months; the interval between visits was then adjusted following assessment of recruitment rate and the number of data queries and serious adverse event (SAE) reports. The study sites were provided with direct access to all trial-related source data and reports for the purpose of monitoring and auditing by the central study team, sponsor and regulatory authorities, as required.

Data and safety monitoring

The DMEC chairperson was responsible for safeguarding the interests of the trial participants and making recommendations to the TSC. The REACT DMEC roles and responsibilities and operating procedures are defined in the REACT DMEC Charter (see *Appendices 2* and *3*). The DMEC was composed of three independent multidisciplinary experts who were not involved in the conduct of the trial in any way. They met prior to the initiation of enrolment and determined a plan to review the protocol, compliance, safety and adverse events (AEs), and outcome data after a prespecified number of infants had been recruited. The TSC was composed of six independent members, whose roles and responsibilities were defined by a charter. The TSC provided advice, through its chairperson, to the chief investigator and reported to the trial sponsor and trial funder.

Safety was assessed continuously during each infant's stay in NICU. The frequency of AEs and SAEs that would normally require reporting within a clinical trial, as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use,[42] was anticipated to be high in the population being studied, despite the low risk of the study intervention. Following discussions with the MHRA and in accordance with regulatory guidance that allows for exceptions in such circumstances, a modified reporting plan was agreed.

Any ADE was recorded and reported to the co-ordinating centre. All device deficiencies that might have led to a SADE if suitable action had not been taken, the intervention had not been made or if circumstances had been less fortunate were reported to the sponsor, as for SAEs and SADEs. AEs were recorded in the notes and captured as exploratory outcomes as part of the CRF. SAEs are known to be common in this population and, therefore, the MHRA requested the following expectations for safety reporting.

During the intervention period of the study (study days 1–7)

The following expected SAEs were required to be recorded in the CRF (safety log) and reported, using the CRF, to the sponsor within 24 hours of awareness of the event: (1) death, (2) culture-positive infection, (3) severe hypoglycaemia (glucose level < 2.6 mmol/l), (4) seizures and (5) any other related SAE.

Post intervention period (study day 8 until end of study)

It was agreed with the MHRA that important medical outcomes, including those normally considered as a SAE for a clinical trial, would be captured in the CRF at the 36 weeks' corrected gestational age assessment (i.e. SAEs were viewed to be anticipated events for this study population and, therefore, they were not required to be recorded or reported separately as a SAE, if judged by the clinical team to be unrelated to the study).

Patient and public involvement

Members of the local parent support group were consulted to help inform trial design. Parents were asked to provide feedback on study involvement as part of the protocol, through both formal review of the protocol/patient information sheet and informal discussions at parent groups within the local NICU. The TSC included a lay person. We sent newsletters to parents to update them on study progress, and an end-of-study update for families.

Dissemination

The findings of the trial have been presented at national meetings, published in international journals and communicated back to the families involved.

Chapter 4 REACT trial results

Recruitment

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in *Figure 5*. A total of 1350 families were screened based on an anticipated birthweight ≤ 1200 g, with 918 families not
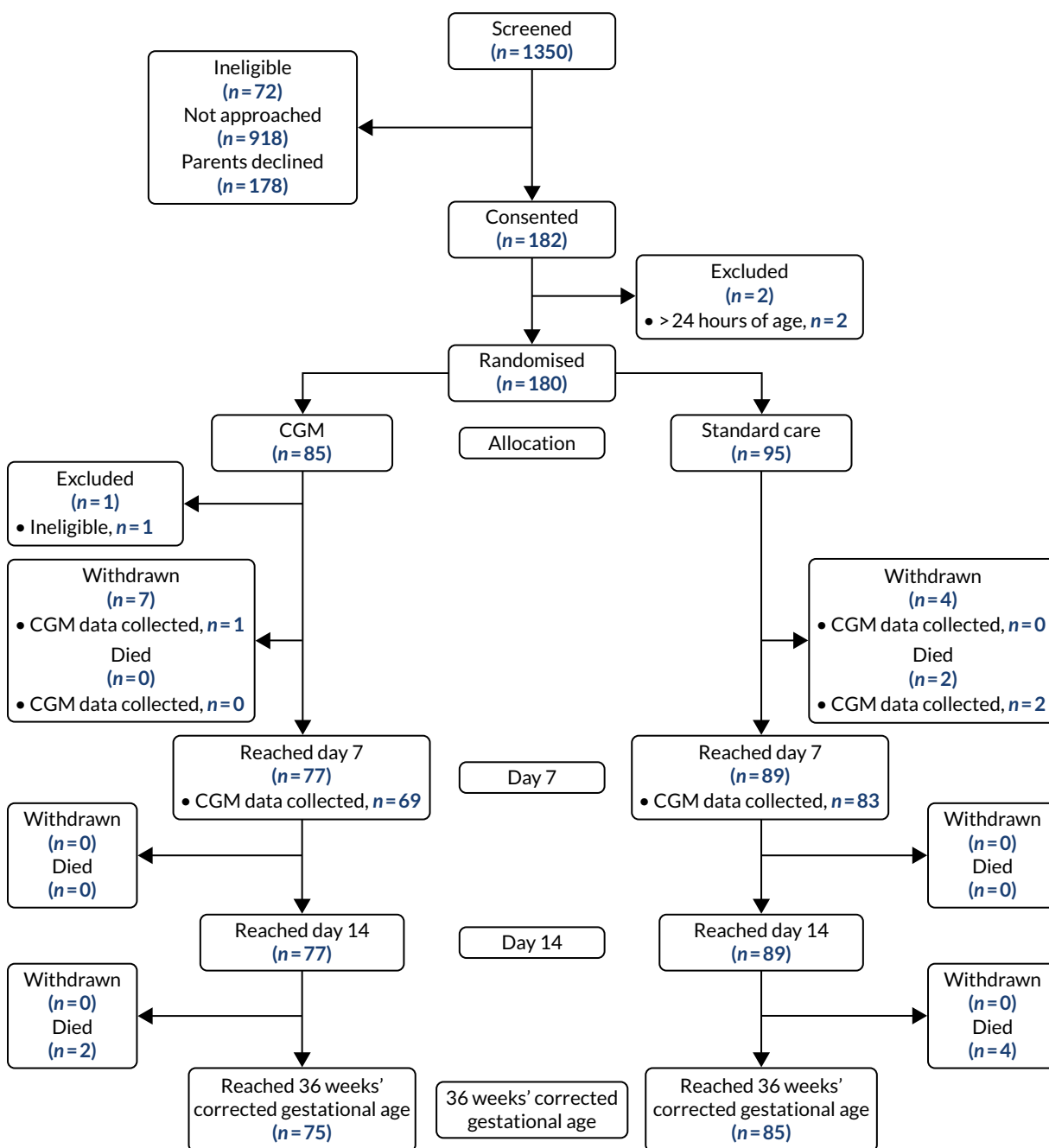
FIGURE 5 A Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Reproduced with permission from Beardsall *et al.*[4] in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

approached because of the short recruiting window of 24 hours. Of the remaining 360 families who were approached, 182 consented, resulting in a consent rate of 51%. Two infants were excluded prior to randomisation, as they were > 24 hours of age. One infant who was found to be ineligible was excluded post randomisation. There were 11 withdrawals from the trial and eight deaths (control, *n* = 6; intervention, *n* = 2).

Demographic details

Demographic details of all recruited infants are provided in *Table 4*. These data show no apparent differences between study arms at baseline in terms of premorbidity and the results are in keeping with what would be anticipated for this preterm population.

TABLE 4 Randomised controlled trial: demographic data

Variable	Statistic	Standard-care arm	CGM arm
Gestational age (weeks)	*n*	95	84
	Mean (SD)	27.4 (1.9)	27.7 (2.1)
Sex, % (*n/N*)	Male	47 (45/95)	54 (45/84)
Ethnicity, % (*n/N*)	Asian	12 (11/95)	8 (7/84)
	Black	8 (8/95)	8 (7/84)
	Mixed	5 (5/95)	7 (6/84)
	Other	5 (5/95)	4 (3/84)
	White	69 (66/95)	73 (61/84)
Number of infants delivered, % (*n/N*)	Singleton	74 (70/95)	77 (65/84)
	Multiple	26 (25/95)	23 (19/84)
CRIB II score	*n*	91	80
	Mean (SD)	10 (2.9)	10 (2.9)
	Median	10	10
	Minimum, maximum	4, 19	4, 19
Birthweight (g)	*n*	95	84
	Mean (SD)	880 (180)	910 (160)
	Median	920	930
	Minimum, maximum	470, 1170	390, 1190
Birthweight SDS	*n*	95	84
	Mean (SD)	−0.8 (0.92)	−0.82 (0.98)
	Median	−0.66	−0.76
	Minimum, maximum	−2.6, 1.32	−2.97, 1.2
Use of antenatal steroids > 24 hours prior to delivery, % (*n/N*)	Yes	73 (69/95)	82 (69/84)
Use of antibiotics in 24 hours prior to delivery, % (*n/N*)	Yes	34 (32/94)	30 (25/84)
Maternal diabetes, % (*n/N*)	Yes	8 (8/95)	6 (5/84)
Maternal chorioamnionitis, % (*n/N*)	Yes	22 (21/95)	23 (19/84)

TABLE 4 Randomised controlled trial: demographic data (*continued*)

Variable	Statistic	Standard-care arm	CGM arm
Delivery mode, % (*n/N*)	Spontaneous vaginal delivery	33 (31/95)	35 (29/84)
	Caesarean section pre onset of labour	42 (40/95)	49 (41/84)
	Caesarean section post onset of labour	23 (22/95)	1 (13/84)
	Assisted vaginal delivery	2 (2/95)	1 (1/84)

CRIB II, Clinical Risk Index for Babies II.
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Compliance with intervention and control procedures

The number of CGM data points in the CGM and standard-care arms was a comparable mean of 1538 (SD 341) and 1412 (SD 424), respectively (*Figure 6*).

In the CGM group, the median number of times sensor glucose was recorded per hour on the CRF was 0.98 (range 0.56–1.45) based on hours' worth of data (number of CGM readings/12) and 0.90 (range 0.29–1.28) based on total sensor duration (hours). The mean percentage of time that the insulin rate of infusion was recorded when the sensor glucose was > 8 mmol/l was 54% (SD 38%). Assessment of compliance with blinding in the control study arm was recorded using a log of time between the tamper tag being opened and resealed. Failure to comply with blinding [prespecified as 12 or more CGM readings available (equivalent to 60 minutes of time) between the tag being opened and resealed] occurred in 15% (14/95) of infants. The median length of time the tags were open for was 0.167 (range 0–23.9) hours, with a mean of 0.377 (SD 1.34) hours. These figures are represented graphically in *Figure 7*.
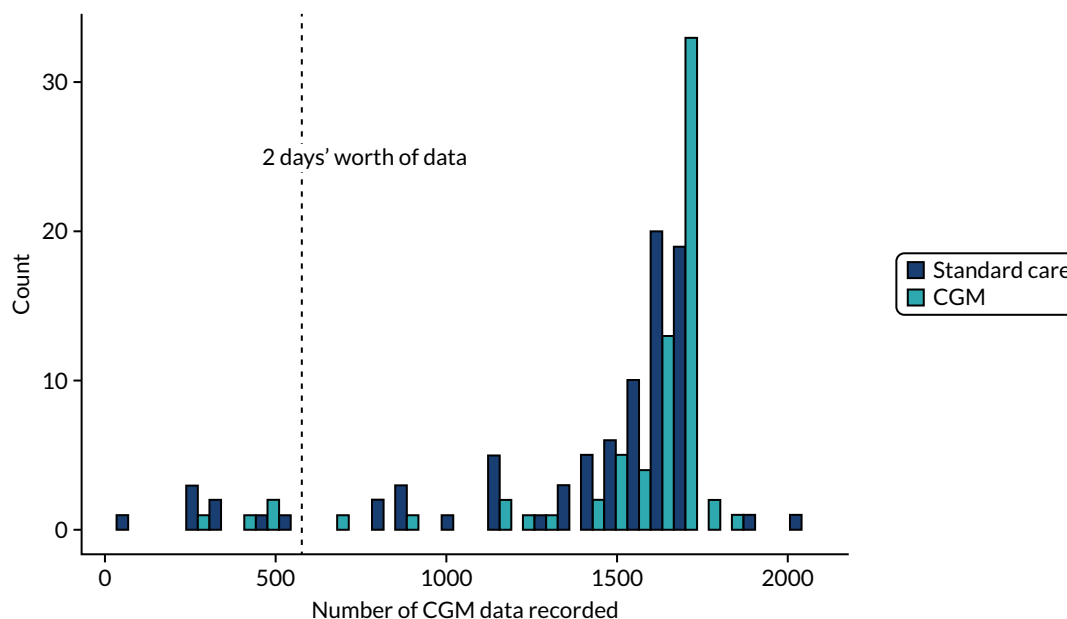
FIGURE 6 Randomised controlled trial: CGM data recorded by treatment group.
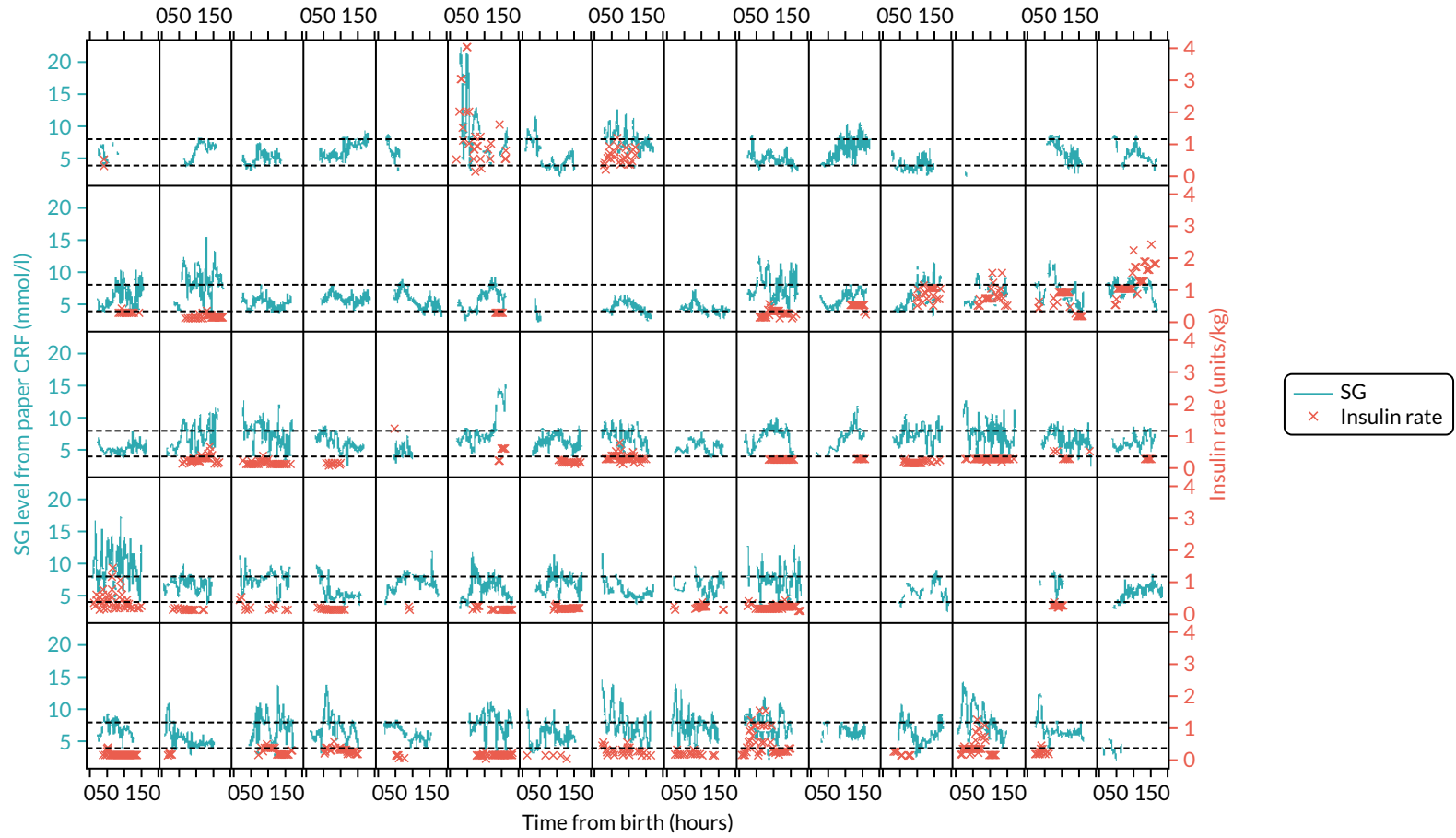
FIGURE 7 Randomised controlled trial: clinically recorded glucose profiles and use of insulin in the CGM intervention study arm. SG, sensor glucose.

Primary outcome measure

The primary results for the full analysis population demonstrated that the time during which sensor glucose was in the target range of 2.6–10 mmol/l was 9% higher in the CGM arm than in the standard-care arm (95% CI 3% to 14%; $p = 0.002$) (*Table 5*). Full model-fitting results exploring the effect of centre and gestation $\geq$ 26 weeks (*Table 6*), and a range of sensitivity analyses (see *Appendix 4, Tables 24* and *25*), all gave similar treatment effects, suggesting that the results are robust. In per-protocol analyses, CGM, compared with standard control, resulted in a 10 percentage-point increase in the time that sensor glucose was in the target range of 2.6–10 mmol/l (95% CI 4% to 17%; $p = 0.002$). Model-fitting results for per-protocol analyses are provided in *Appendix 4, Table 25*.

Significant subgroup effects included sex (compared with standard care, CGM resulted in a 15 percentage-point increase in the time that sensor glucose level was in the target range in male infants and a 2 percentage-point increase in female infants; see *Appendix 4, Table 26*).

TABLE 5 Randomised controlled trial: primary and secondary efficacy

Variable	Statistic	Standard-care arm	CGM arm	Linear regression model	
				Adjusted mean difference[a] (95% CI)	p-value
Percentage of time sensor glucose is in target range of 2.6–10 mmol/l	n	85	70	8.9 (3.4 to 14.4)	0.002
	Mean (SD)	84 (22)	94 (11)		
	Median	97	99		
	Minimum, maximum	14, 100	51, 100		
Mean sensor glucose level (mmol/l)	n	85	70	−0.46 (−1 to 0.09)	0.99
	Mean (SD)	7 (2.1)	6.5 (1.2)		
	Median	6.5	6.4		
	Minimum, maximum	3.1, 12.2	3, 9.9		
Percentage of time sensor glucose is in target range of 4–8 mmol/l	n	85	70	11.5 (3.7 to 19.2)	0.004
	Mean (SD)	62 (29)	74 (20)		
	Median	65	78		
	Minimum, maximum	0, 100	16, 100		
Sensor glucose variability (mmol/l)	n	85	70	−0.01 (−0.15 to 0.13)	0.9
	Mean (SD)	3.6 (4.3)	2.7 (3)		
	Median	2.1	1.9		
	Minimum, maximum	0.07, 22	0.6, 23.1		
Percentage of time in hyperglycaemic range (i.e. > 15 mmol/l)	n	85	70	−0.92 (−2.03 to 0.19)	0.1
	Mean (SD)	1.3 (4.2)	0.3 (2.1)		
	Median	0	0		
	Minimum, maximum	0, 24	0, 16		

a Adjusted for centre and gestation (< 26 weeks' gestation, $\geq$ 26 weeks' gestation).

TABLE 6 Randomised controlled trial: model-fitting results – primary analysis

Outcome	Covariate	Estimate (SE)	95% CI	p-value
Percentage of time sensor glucose is in the target range 2.6–10 mmol/l	Intercept	80.6 (3.7)	73.4 to 87.9	< 0.001
	CGM vs. standard care	8.9 (2.8)	3.4 to 14.4	0.002
	N36 (reference N01)	−7.9 (12.3)	−32.2 to 16.5	0.5
	N42	7.6 (5.9)	−4.1 to 19.3	0.2
	N43	0.2 (4.2)	−8.2 to 8.6	0.96
	N68	0.2 (4.2)	−8.1 to 8.5	0.97
	N73	0.3 (5.5)	−10.6 to 11.2	0.95
	N74	10 (12)	−14 to 34	0.4
	N85	8.2 (6.9)	−5.4 to 21.8	0.2
	N86	−16 (8.9)	−33.7 to 1.6	0.08
	N87	−12.2 (12.4)	−36.6 to 12.2	0.3
	N88	−29 (8)	−44.8 to −13.2	< 0.001
	ND3	6.9 (6.9)	−6.7 to 20.5	0.3
	SP3	9.6 (8.9)	−8 to 27.2	0.3
	Gestation ≥ 26 weeks	4.9 (3.6)	−2.1 to 12	0.2

RSD = 17.02

RSD, residual error standard deviation; SE, standard error.

Secondary outcomes

Efficacy

Secondary outcome analyses showed that time in the target range of 4–8 mmol/ was 12 percentage-points higher in the CGM arm than in the standard-care arm. The mean sensor glucose level, sensor glucose variability and percentage of time sensor glucose level was > 15 mmol/l were all lower in the CGM arm than in the standard-care arm, but none of these differences reached statistical significance. Results are provided with multiple testing procedure data (see *Appendix 4, Table 27*).

Safety

Continuous glucose monitor data showed that more infants in the standard-care arm (15%) than in the CGM arm (6%) were exposed to at least one episode of sensor glucose < 2.6 mmol/l for > 1 hour. Safety outcome data are provided in *Table 7*. AEs and ADEs are reported in *Tables 8* and *9*, respectively. The tables show that episodes of blood glucose levels ≤ 2.2 mmol/l and 2.2–2.6 mmol/l occurred in 7% and 12%, respectively, of the standard-care group, and in 13% and 15%, respectively, of the CGM group. Collection of the blood glucose data was biased by the result of a low sensor glucose level in the CGM arm, prompting blood glucose to be checked, and is reflected in the higher percentage of infants in the standard-care arm who were exposed to at least one episode of hypoglycaemia lasting > 1 hour. Owing to the small numbers and interinfant variability, none of these differences was statistically significant.

The mean percentage of time for which sensor glucose level was < 2.6 mmol/l was 1% (SD 3.2%) in the standard-care group and 1% (SD 5.3%) in the CGM group. The percentage of time that sensor glucose level was < 2.6 mmol/l depended on the number of CGM data available, which explains why it is similar in both groups, despite the total length of time that sensor glucose level was < 2.6 mmol/l being greater in the standard-care arm. Further details of SAEs and SADEs are provided in *Tables 8* and *9*, and details of withdrawals from the intervention or study, and deaths are shown in *Appendix 4, Tables 28–30*.

TABLE 7 Randomised controlled trial: safety analyses of CGM vs. standard care

Variable	Statistic	Standard-care arm	CGM arm	Logistic regression Adjusted OR[a] (95% CI)	p-value
Blood glucose level range 2.2–2.6 mmol/l		12% (11/93)	15% (11/75)	1.2 (0.48 to 3.2)	0.7
Blood glucose level ≤ 2.2 mmol/l		7% (6/93)	13% (10/75)	2.2 (0.7 to 7.1)	0.2
Continuous episode of sensor glucose < 2.6 mmol/l for > 1 hour		15% (13/85)	6% (4/70)	0.361 (0.0919 to 1.2)	0.1
Length of time sensor glucose level is < 2.6 mmol/l (hours)	n	85	70		
	Mean (SD)	1.0 (3.2)	0.5 (1.7)		
	Median	0	0		
	Minimum, maximum	0, 22	0, 11.2		
Percentage of time that the sensor glucose level is < 2.6 mmol/l	n	85	70		
	Mean (SD)	1.1 (3.2)	1 (5.3)		
	Median	0	0		
	Minimum, maximum	0, 17	0, 41		

OR, odds ratio.
a Adjusted for centre and gestation (< 26 weeks' gestation, ≥ 26 weeks' gestation).
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TABLE 8 Randomised controlled trial: AE reporting

Variable	Statistic	Standard-care arm, % (n/N)	CGM arm, % (n/N)	Total, % (n/N)
AE description	Culture-positive infection	0 (0/95)	1 (1/84)	1 (1/179)
	Moderate hypoglycaemia (sensor): sensor glucose 2.2–2.6 mmol/l for > 1 hour	0 (0/95)	6 (5/84)	3 (5/179)
	Moderate hypoglycaemia: blood glucose level range 2.2–2.6 mmol/l	9 (9/95)	6 (5/84)	8 (14/179)
	Persistent pulmonary hypertension	1 (1/95)	0 (0/84)	1 (1/179)
	Pulmonary haemorrhage	1 (1/95)	0 (0/84)	1 (1/179)
	Seizures	1 (1/95)	0 (0/84)	1 (1/179)
	Severe hypoglycaemia: blood glucose level ≤ 2.2 mmol/l	5 (5/95)	10 (8/84)	7 (13/179)
	Severe prematurity	2 (2/95)	0 (0/84)	1 (2/179)
	Transient: sensor glucose level < 2.6 mmol/l for < 1 hour	0 (0/95)	2 (2/84)	1 (2/179)

Utility

Table 10 shows summary statistics for the number of sensors used, the individual sensor duration and the number of CGM data collected (hours). We received CGM data from 155 infants, with loss of data due to reported failure of sensor insertion, calibration failure and lack of data at download. Insertion of the first sensor failed in 18% of infants and, therefore, the average number of sensors needed per infant was 1.2. Details of withdrawals are provided in *Appendix 4*, *Tables 28* and *29*. The success of sensor insertion varied markedly between centres. Difficulties in calibrating the sensor with the blood

TABLE 9 Randomised controlled trial: ADEs reporting

Variable	Statistic	Standard-care arm, % (n/N)	CGM arm, % (n/N)	Total, % (n/N)
ADE description	Bruising at sensor site	3 (3/95)	4 (3/84)	3 (6/179)
	Clinically significant discrepancy between sensor glucose and blood glucose levels	0 (0/95)	8 (7/84)	4 (7/179)
	Excoriated skin at sensor site	1 (1/95)	0 (0/84)	1 (1/179)
	Failure to re-establish connectivity during intervention	4 (4/95)	2 (2/84)	3 (6/179)
	Failure to transmit data to the MiniMed 640G because of loss of connectivity	7 (7/95)	6 (5/84)	7 (12/179)
	Pressure mark on skin	2 (2/95)	0 (0/84)	1 (2/179)
	Sensor displaced	1 (1/95)	2 (2/84)	2 (3/179)
	Sensor insertion failure	22 (21/95)	13 (11/84)	18 (32/179)
	Transient: sensor glucose level < 2.6 mmol/l for < 1 hour	0 (0/95)	2 (2/84)	1 (2/179)
	Unable to calibrate	23 (22/95)	20 (17/84)	22 (39/179)
	User error	1 (1/95)	0 (0/84)	1 (1/179)

TABLE 10 Randomised controlled trial: duration of sensor use

Variable	Statistic	Standard-care arm	CGM arm	Total
Sensor duration (hours)	n	92	81	173
	Mean (SD)	128 (47)	127 (48)	127 (48)
	Median	145	145	145
	Minimum, maximum	4, 192	2, 191	2, 192
Number of CGM data (hours)	n	85	70	155
	Mean (SD)	118 (35)	128 (28)	122 (33)
	Median	133	140	136
	Minimum, maximum	6, 170	24, 155	6, 170
Number of sensors used	n	95	84	179
	Mean (SD)	1.25 (0.48)	1.13 (0.43)	1.20 (0.46)
	Median	1	1	1
	Minimum, maximum	0, 3	0, 2	0, 3

glucose level were reported in 22% of infants and episodes where data could not be linked between the transmitter and monitor occurred in 7% of infants. ADEs reported included bruising at the sensor site in 3% of infants, and significant discrepancy between sensor glucose and blood glucose in seven (4%) infants in the CGM study arm. In three infants, the sensor became displaced from under the skin (fell out).

The staff and parent questionnaire results are presented in *Figures 8* and *9*, respectively. Most staff found the devices easy to calibrate (86%) and did not think that the CGM device interfered with the infant's nursing care (87%) or caused any distress (94%). Seventy per cent of staff felt that the use of CGM improved clinical care. The majority of parents reported that the CGM did not interfere with the infant's nursing care (96%) or cause any distress (89%), and 80% felt that the use of CGM improved clinical care.
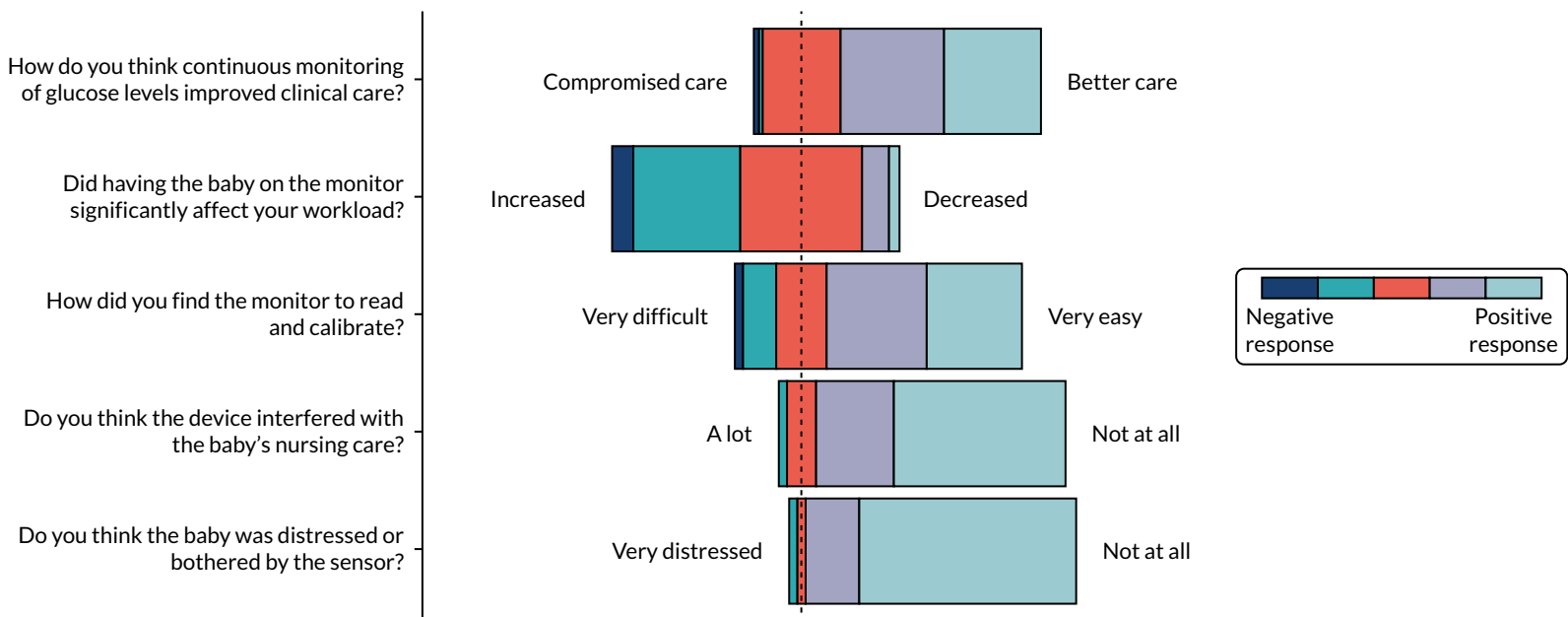
FIGURE 8 Randomised controlled trial: staff questionnaires of utility. Stacked bar chart showing proportion of response for each Likert question. Reproduced with permission from Beardsall et al.[4] in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.
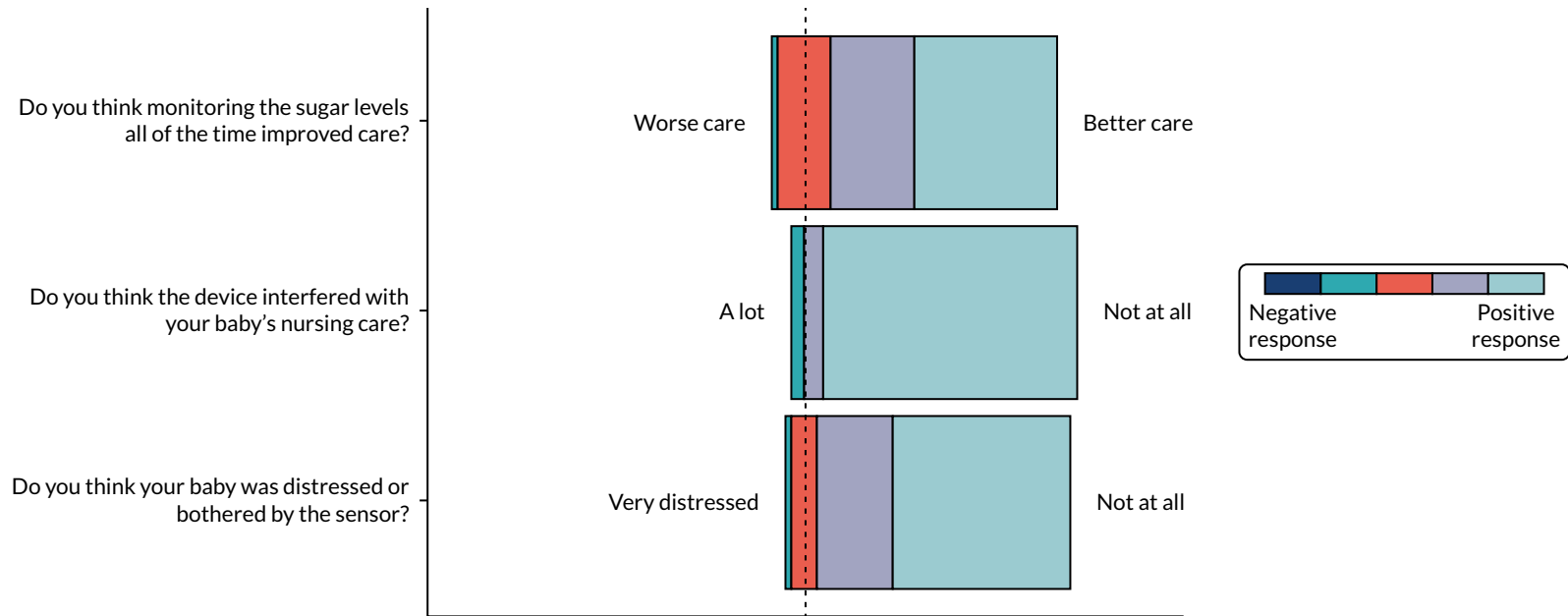
FIGURE 9 Randomised controlled trial: parent questionnaire of acceptability. Stacked bar chart showing proportion of response for each Likert question. Reproduced with permission from Beardsall *et al.*[4] in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Concomitant medications

Details of complementary medical treatment received during the intervention period in both study arms are provided in *Table 11*. These data are in keeping with what would be considered standard clinical care for this population and there were no apparent differences between study arms.

TABLE 11 Randomised controlled trial: medications given during days 1–7

Variable	Statistic	Standard-care arm	CGM arm	Total
Inotropes given (days)	*n*	94	80	174
	Mean (SD)	0.8 (1.6)	0.7 (1.5)	0.7 (1.5)
	Median	0	0	0
	Minimum, maximum	0, 7	0, 7	0, 7
Antibiotics given (days)	*n*	94	80	174
	Mean (SD)	4.3 (2.3)	4.5 (2.4)	4.4 (2.4)
	Median	4	5	5
	Minimum, maximum	0, 7	0, 7	0, 7
Caffeine given (days)	*n*	94	80	174
	Mean (SD)	6.4 (1.6)	6.6 (1.4)	6.5 (1.5)
	Median	7	7	7
	Minimum, maximum	1, 7	1, 7	1, 7
Morphine given (days)	*n*	94	80	174
	Mean (SD)	1.7 (2.5)	1.8 (2.6)	1.7 (2.5)
	Median	0	0	0
	Minimum, maximum	0, 7	0, 7	0, 7
Corticosteroids given (days)	*n*	94	80	174
	Mean (SD)	0.12 (0.53)	0.09 (0.51)	0.1 (0.52)
	Median	0	0	0
	Minimum, maximum	0, 4	0, 4	0, 4
Insulin given (days)	*n*	94	80	174
	Mean (SD)	1.6 (2.4)	2.6 (2.5)	2.1 (2.5)
	Median	0	2.5	0
	Minimum, maximum	0, 7	0, 7	0, 7
Insulin units, days 1–7 (per kg per day)	*n*	94	80	174
	Mean (SD)	0.6 (2.1)	0.6 (0.94)	0.6 (1.7)
	Median	0	0.19	0
	Minimum, maximum	0, 19.8	0, 5.39	0, 19.8
Insulin units, days 8–14 (per kg per day)	*n*	88	75	163
	Mean (SD)	0.15 (0.34)	0.16 (0.43)	0.16 (0.38)
	Median	0	0	0
	Minimum, maximum	0, 1.72	0, 2.83	0, 2.83
Glucose (g/kg/day)	*n*	95	84	179
	Mean (SD)	9.1 (2.6)	9.5 (3.1)	9.3 (2.9)
	Median	9.3	10.1	9.9
	Minimum, maximum	0, 14.9	0, 17.2	0, 17.2

continued

TABLE 11 Randomised controlled trial: medications given during days 1–7 (*continued*)

Variable	Statistic	Standard-care arm	CGM arm	Total
Glucose (ml/kg/day)	*n*	95	84	179
	Mean (SD)	84 (24)	85 (28)	84 (26)
	Median	86	92	88
	Minimum, maximum	0, 143	0, 185	0, 185
Lipids (g/kg/day)	*n*	92	80	172
	Mean (SD)	1.95 (0.78)	1.89 (0.77)	1.92 (0.78)
	Median	2.1	1.95	2
	Minimum, maximum	0.04, 3.9	0.04, 4.7	0.04, 4.7
Lipids (ml/kg/day)	*n*	92	80	172
	Mean (SD)	9.9 (3.7)	9.7 (3.7)	9.8 (3.7)
	Median	10.6	9.9	10.4
	Minimum, maximum	1.8, 19.5	1.9, 23.7	1.8, 23.7
Amino acids (g/kg/day)	*n*	94	81	175
	Mean (SD)	2.2 (1.3)	2.2 (1.2)	2.2 (1.3)
	Median	2.4	2.5	2.5
	Minimum, maximum	0, 7.2	0, 6.1	0, 7.2
Oral nutrition (ml/kg/day)	*n*	94	81	175
	Mean (SD)	18 (23)	20 (21)	19 (22)
	Median	11	14	12
	Minimum, maximum	0, 108	0, 94	0, 108

Exploratory outcome measures

Further data on glucose profiles in the CGM and standard-care arms are provided in *Figures 10* and *11*, respectively.

Exploratory analyses of the use of insulin can be found in *Figure 12*. *Figure 12* shows that variability in the use of insulin during study days 5–7 was greater in the standard-care arm than in the CGM arm. There were no differences in any of the growth parameters between study arms at any study time points.

Details of causes of death are provided in *Appendix 4, Table 30*. Details of growth parameters are provided in *Appendix 4* for at birth (see *Appendix 4, Table 31*), day 7 (see *Appendix 4, Table 32*), day 14 (see *Appendix 4, Table 33*) and at 36 weeks' corrected gestational age (see *Appendix 4 Table 34*). Changes in growth SDS are provided from birth to 36 weeks' corrected gestational age for weight (*Figure 13*), body length (*Figure 14*) and head circumference (*Figure 15*).
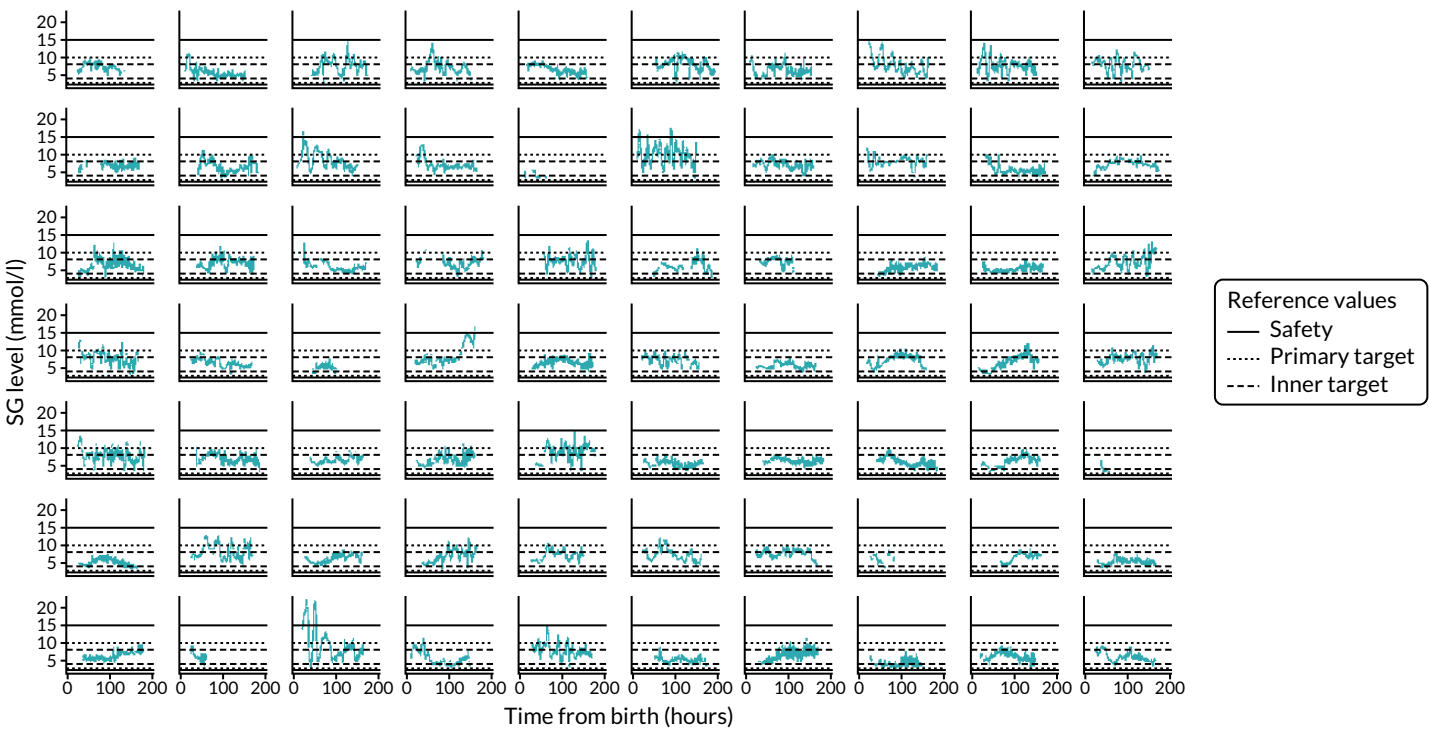
FIGURE 10 Randomised controlled trial: profile plots of CGM data – CGM arm. SG, sensor glucose.
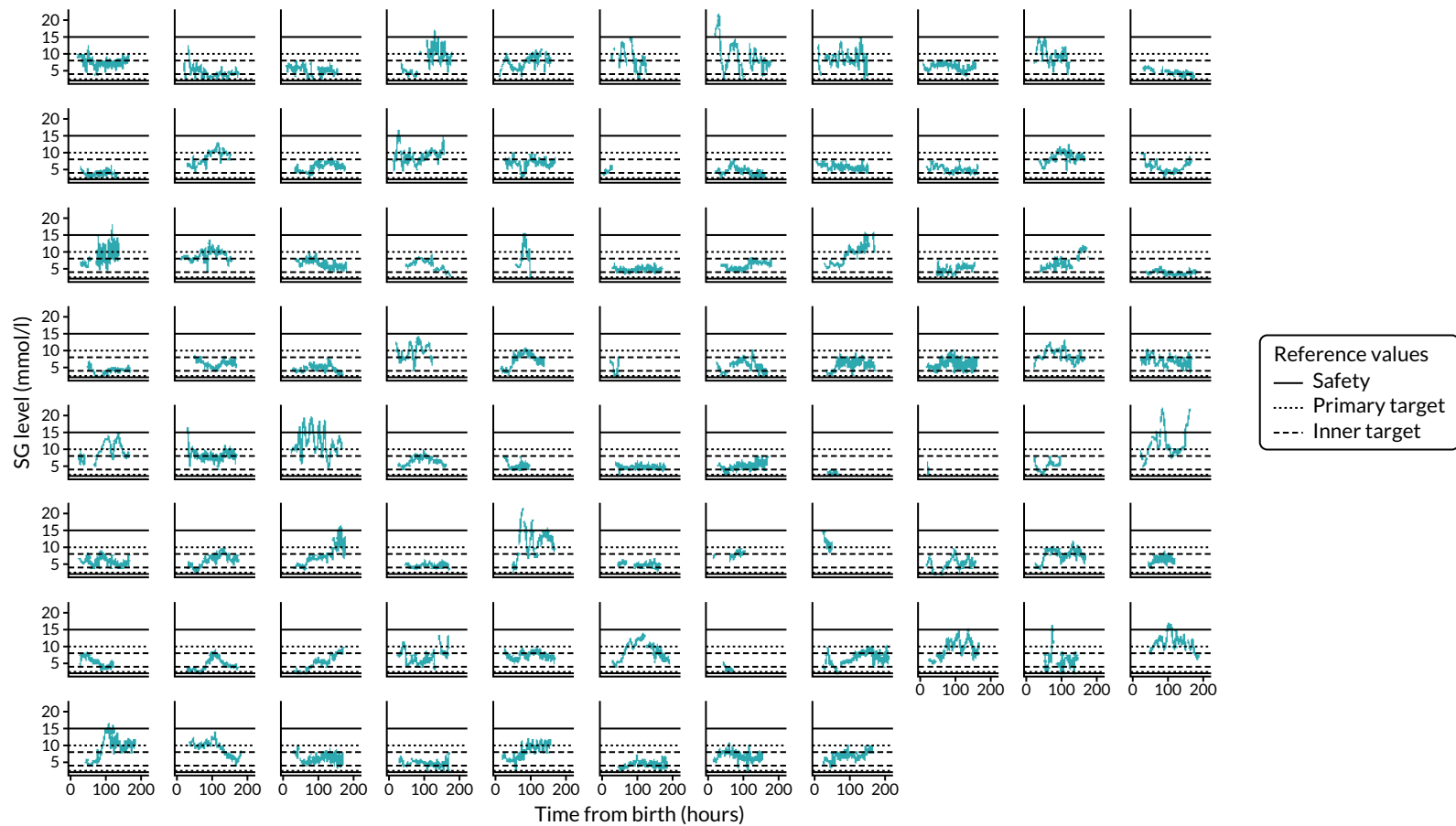
FIGURE 11 Randomised controlled trial: profile plots of CGM data – standard-care arm. SG, sensor glucose.
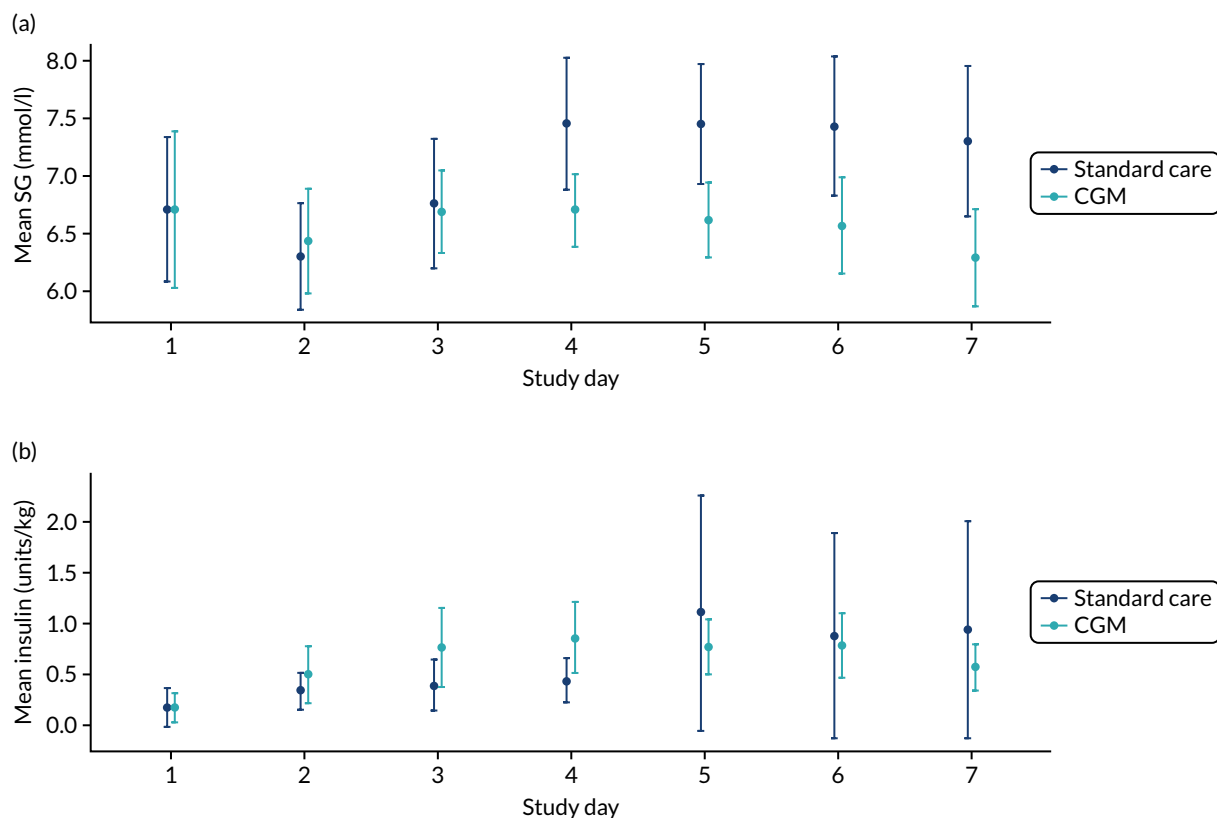
FIGURE 12 Randomised controlled trial: mean (95% CI) insulin and sensor glucose against study day. (a) Sensor glucose; and (b) insulin. SG, sensor glucose.
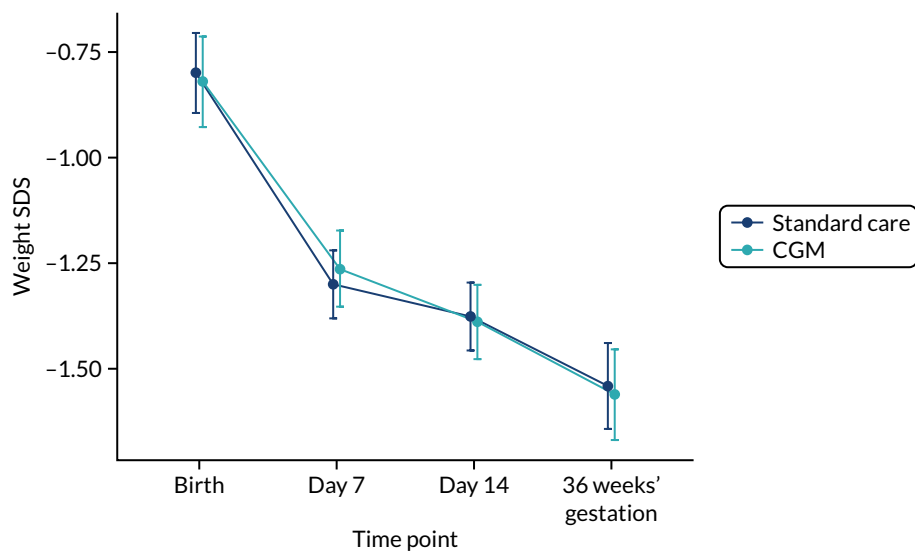
FIGURE 13 Randomised controlled trial: change in mean weight SDS over time. Error bars represent standard error of the mean.
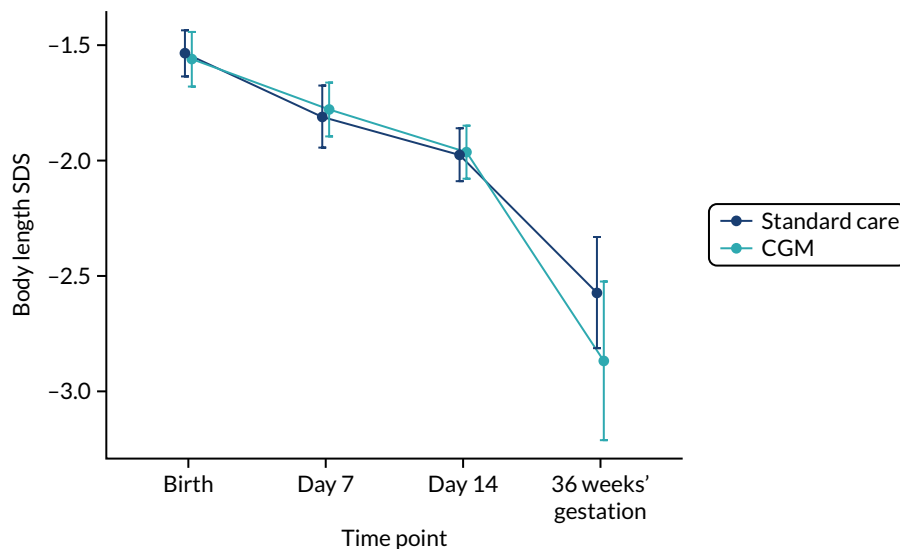
FIGURE 14 Randomised controlled trial: mean body length SDS over time. Error bars represent standard error of the mean.
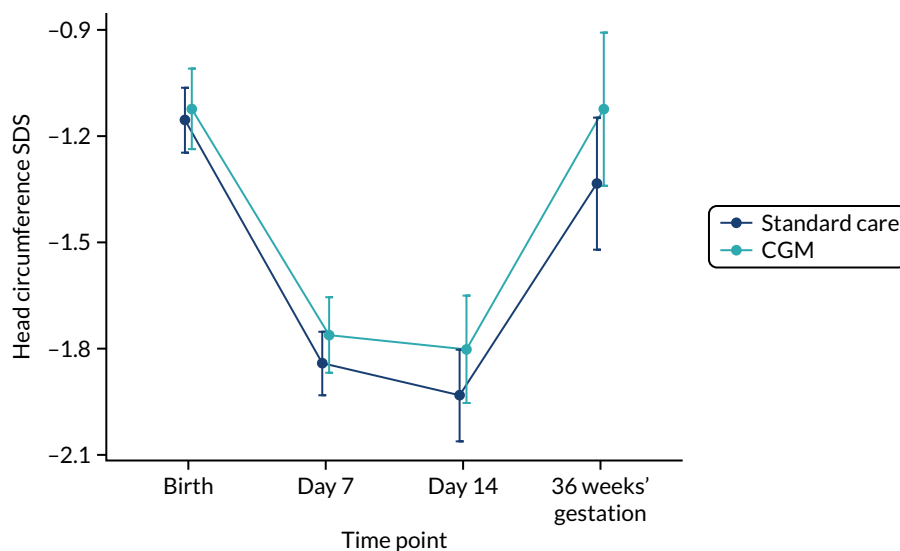
FIGURE 15 Randomised controlled trial: change in mean head circumference SDS over time. Error bars represent standard error of the mean.

Summary statistics of the exploratory clinical outcomes analyses and model fitting are provided in *Tables 12* and *13*, respectively. More infants in the standard-care arm (12%) than in the CGM arm (5%) required surgery for PDA, but the difference did not reach statistical significance. CGM was associated with a significant reduction in the exploratory outcome of NEC as 28% of infants in the standard-care arm were diagnosed with NEC, compared with 13% of infants in the CGM arm [odds ratio (OR) 0.33, 95% CI 0.13 to 0.78; $p = 0.01$].

TABLE 12 Randomised controlled trial: summary statistics of exploratory outcomes

Variable	Statistic	Standard-care arm	CGM arm	Total
Mortality, % (*n/N*)	Yes	6 (6/95)	2 (2/84)	4 (8/179)
Maximum severity of ROP	*n*	78	68	146
	Mean (SD)	1.5 (3.6)	1.1 (3.8)	1.3 (3.7)
	Median	0	0	0
	Minimum, maximum	0, 22	0, 22	0, 22
Maximum severity of ROP (categorical), % (*n/N*)	< 3	88 (69/78)	96 (65/68)	92 (134/146)
	≥ 3	12 (9/78)	4 (3/68)	8 (12/146)
BPD, % (*n/N*)	Yes	66 (56/85)	60 (45/75)	63 (101/160)
BPD severity, % (*n/N*)	Mild	32 (18/56)	22 (10/45)	28 (28/101)
	Moderate	46 (26/56)	64 (29/45)	54 (55/101)
	Severe	21 (12/56)	13 (6/45)	18 (18/101)
Infection, % (*n/N*)	Yes	62 (53/85)	68 (50/74)	65 (103/159)
NEC requiring medical or surgical treatment, % (*n/N*)	Yes	28 (24/85)	13 (10/75)	21 (34/160)
NEC treatment, % (*n/N*)	Medically managed	83 (20/24)	80 (8/10)	82 (28/34)
	Surgically managed	17 (4/24)	20 (2/10)	18 (6/34)
PDA requiring medical or surgical treatment, % (*n/N*)	Yes	31 (26/85)	26 (19/74)	28 (45/159)
PDA treatment, % (*n/N*)	Medically managed	88 (23/26)	95 (18/19)	91 (41/45)
	Surgically managed	12 (3/26)	5 (1/19)	9 (4/45)
Intracerebral pathology, % (*n/N*)	Yes	32 (27/84)	33 (25/75)	33 (52/159)
Intracerebral pathology type, % (*n/N*)	Germinal layer haemorrhage	44 (12/27)	40 (10/25)	42 (22/52)
	IVH without ventricular dilatation	33 (9/27)	44 (11/25)	38 (20/52)
	IVH with ventricular dilatation	26 (7/27)	32 (8/25)	29 (15/52)
	Parenchymal involvement	22 (6/27)	12 (3/25)	17 (9/52)

IVH, intraventricular haemorrhage.

TABLE 13 Randomised controlled trial: model-fitting results of exploratory outcomes

Model	Outcome	Covariate	Estimate (SE)[a]	95% CI	p-value
Linear regression	Maximum ROP	Intercept	2.53 (0.78)	0.98 to 4.08	0.002
		CGM vs. standard care	–0.26 (0.56)	–1.37 to 0.85	0.6
	Weight SDS, day 7	Intercept	–0.88 (0.16)	–1.19 to –0.57	< 0.001
		CGM vs. standard care	0.05 (0.12)	–0.19 to 0.28	0.7
	Weight SDS, 36 weeks' gestational age	Intercept	–1.17 (0.21)	–1.59 to –0.76	< 0.001
		CGM vs. standard care	–0.04 (0.15)	–0.34 to 0.25	0.8
	Body length SDS, day 7	Intercept	–1.72 (0.22)	–2.15 to –1.28	< 0.001
		CGM vs. standard care	–0.02 (0.17)	–0.36 to 0.31	0.9
	Body length SDS, 36 weeks' gestational age	Intercept	–4.05 (0.67)	–5.4 to –2.7	< 0.001
		CGM vs. standard care	–0.38 (0.4)	–1.19 to 0.42	0.3
	Head circumference, day 7	Intercept	–1.59 (0.17)	–1.93 to –1.25	< 0.001
		CGM vs. standard care	0.07 (0.14)	–0.2 to 0.35	0.6
	Head circumference, 36 weeks' gestational age	Intercept	–2.14 (0.4)	–2.94 to –1.35	< 0.001
		CGM vs. standard care	0.13 (0.29)	–0.44 to 0.7	0.6
	Daily glucose (g/kg)	Intercept	9.53 (0.55)	8.44 to 10.6	< 0.001
		CGM vs. standard care	0.42 (0.41)	–0.39 to 1.22	0.3
	Daily amino acids (g/kg)	Intercept	2.59 (0.16)	2.29 to 2.9	< 0.001
		CGM vs. standard care	0.17 (0.12)	–0.06 to 0.4	0.2
	Daily lipids (g/kg)	Intercept	1.67 (0.12)	1.44 to 1.9	< 0.001
		CGM vs. standard	–0.04 (0.09)	–0.21 to 0.13	0.6
	Daily oral nutrition (ml/kg/d)	Intercept	5.9 (3.8)	–1.6 to 13.4	0.1
		CGM vs. standard care	2 (2.8)	–3.6 to 7.6	0.5
	Total insulin, week 1 (units/kg)	Intercept	8 (2.3)	3.4 to 12.5	< 0.001
		CGM vs. standard care	0.08 (1.7)	–3.3 to 3.5	0.96
	Total insulin, week 2 (units/kg)	Intercept	2 (0.58)	0.89 to 3.2	< 0.001
		CGM vs. standard care	0.1 (0.44)	–0.76 to 0.96	0.8
Logistic regression	Mortality	CGM vs. standard care	0.263 [0.23]	0.0353 to 1.3	0.1
	Infection	CGM vs. standard care	1 [0.4]	0.46 to 2.2	0.99
	NEC	CGM vs. standard care	0.328 [0.15]	0.129 to 0.78	0.01
	PDA	CGM vs. standard care	0.52 [0.243]	0.199 to 1.3	0.2
	Intracerebral pathology	CGM vs. standard care	1.02 [0.365]	0.51 to 2.1	0.9
Ordinal logistic regression	BPD	CGM vs. standard care	1.2 [3.2]	0.52 to 2.8	0.7

SE, standard error.
a OR [SE(OR)]. Analyses adjusted for centre and gestation.

Chapter 5 REACT randomised controlled trial health economic analyses

Parts of this text have been reprinted from *Seminars in Perinatology*, vol. 45, Petrou S, Kim S, Bond S, Allison A, Beardsall K, the REACT collaborative, Cost-effectiveness of real time continuous glucose monitoring to target glucose control in preterm infants, pp. 151392, Copyright (2021),[43] with permission from Elsevier.

Introduction

The main goal of the health economic evaluation for the REACT RCT was to evaluate the comparative cost-effectiveness of the two interventions (CGM and standard care) in preterm infants weighing ≤ 1200 g and aged ≤ 24 hours. The economic analysis adopted a NHS and Personal Social Services (PSS) perspective in accordance with the National Institute for Health and Care Excellence (NICE) methodological recommendations.[44] For the purposes of the economic evaluation, cost-effectiveness was primarily presented in terms of incremental cost per additional case of adequate glucose control during the first 6 days of life for the trial participants. However, clinical data were prospectively collected until 36 weeks' corrected gestational age. As a result, the costs incurred until 36 weeks and secondary outcomes were also reflected in the cost-effectiveness analysis. Study participants were hospitalised in a NICU and the majority of participants were in hospital at the 36 weeks' corrected gestational age assessment. The time horizon covered the period from randomisation to the end of follow-up at the 36 weeks' corrected gestational age assessment. Costs and outcomes were therefore not discounted because of the short time horizon of the economic evaluation, extending to either 7 days' or 36 weeks' corrected gestational age.

Methods

Measurement of resource use and costs
Health economic data were collected on:

- resource use and costs associated with CGM (i.e. direct intervention costs)
- broader health service use during the 36-week follow-up period.

All costs were presented in Great British pounds and valued in 2016–17 prices. If necessary, costs were inflated or deflated to 2016–17 prices using the Hospital and Community Health Services Pay and Price Inflation Index.[45]

Direct intervention costs
Direct intervention costs encompassed the costs associated with the application of the comparator intervention (i.e. CGM with guideline) over and above the cost of standard care. Infants in the CGM arm were fitted with Enlite glucose sensors, which were linked to a MiniMed 640G System and calibrated with POC blood glucose levels. As a result, the costs of the intervention included the cost of the Enlite sensor and MiniMed 640G System, the costs associated with fitting the device to infants (hospital staff time) and the costs associated with the removal of sensors. The lifetime cost of the Medtronic plc system was annuitised and then further adjusted to reflect the duration of use of the device over the trial period. However, to reflect clinical practice outside the confines of a RCT, the resource inputs associated with masked CGM and the use of associated devices were not costed in the standard-care arm, although the relevant resource inputs were prospectively measured. The resource use associated with the direct intervention costs was collected prospectively. *Table 14* provides an outline of the types of direct intervention-related resource inputs that were measured and the sources of the unit costs of each resource input.

TABLE 14 Randomised controlled trial: direct intervention costs

Resource type	Resource use	Unit cost source
Medtronic plc MiniMed 640G System and Enlite sensors	Cost of MiniMed 640G System and Enlite sensors	Manufacturers
Enlite sensor insertion and set-up of MiniMed 640G System	Staff time	NHS Agenda for Change[46] and clinician's advice
Sensor glucose monitoring	Staff time	NHS Agenda for Change[46] and clinician's advice
Removal of sensor	Staff time	NHS Agenda for Change[46] and clinician's advice
POC (StatStrip)	Cost of Nova Biomedical devices	Manufacturers

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Cost estimates for staff inputs associated with key clinical events, such as time associated with sensor insertion and removal, were based on expert clinical advice about the duration of each event, and the unit cost values for staff inputs were obtained from the NHS Agenda for Change 2016/17 pay scales.[46]

The total direct intervention cost for each participant was estimated by estimating the compound of the associated resource use input values multiplied by their unit cost values.

Measuring broader resource use

The different types of resource categories for broader health-care costs and the sources of their unit costs are presented in *Table 15*.

Broader resource use data were collected for each infant using data extraction sheets that were completed by research nurses in each clinical centre. The nurses extracted the relevant data directly from routine hospital systems and patient records following the final follow-up assessments at

TABLE 15 Randomised controlled trial: broader health-care and social costs

Resource type	Resource use	Unit cost source
Length of stay by level of care (e.g. intensive care, special care)	Staff salaries, on-costs, equipment, consumables, revenue and capital overheads	NHS reference costs[47]
Medications	Cost of medications	BNF[48]
Investigations	Staff time to deliver the investigations, associated costs	NHS reference costs[47]
Medical (surgical) treatment	Staff time to deliver treatment, associated costs	NHS reference costs[47]
Blood transfusion products	Cost of blood transfusion products	*NHS Blood and Transplant Price List 2017*[49]
Surgical procedures	Staff time to deliver the interventions, associated costs	NHS reference costs;[47] NHS Agenda for Change[46]
Mode of discharge	Mode and distance of transfer or discharge to home	UK government[50]

BNF, *British National Formulary*.
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36 weeks' corrected gestational age. The CRFs recorded details of length of inpatient stays by intensity of care, investigations performed [e.g. ultrasound scan, magnetic resonance imaging (MRI), electrocardiography (ECG), computed tomography (CT) scan, X-ray, cranial ultrasound scan and electroencephalography (EEG)], medications and procedures performed (e.g. lumbar punctures, ventricular taps, long lines, surgical procedures and interventions for ROP treatment). The CRFs also captured information surrounding transfers between hospitals, and the modes of transport used for hospital transfers and at final hospital discharge. Distances associated with transfers between hospitals were calculated using Google Maps (Google Inc., Mountain View, CA, USA).

Valuation of resource use
Unit cost data were mainly based on NHS reference costs.[47]

Costs for sensor insertion, sensor monitoring and sensor removal were calculated by multiplying the duration of each activity, based on clinical advice, by the unit cost extracted from the NHS Agenda for Change pay scales (2016/17).[46] The costs of medications for infants were estimated based on the doses and frequencies reported on the CRF, with medication costs obtained from the *British National Formulary*.[48] The costs of blood transfusion products, such as platelets, red blood cells and frozen plasma, were obtained from *NHS Blood and Transplant Price List 2017*[49] and multiplied by the volume of each product used.

When infants were transferred to another hospital, the distance (miles) between the study site and transferred location was calculated using Google Maps and fuel costs were calculated using the advisory fuel rates obtained from the UK government.[50] The fuel costs applied to the distances of hospital transfers in clinical sites located outside the UK were estimated in the same manner.

Measurement of outcomes
The primary clinical outcome measure for this study was the percentage of time sensor glucose readings were within the target range of 2.6–10 mmol/l during the first 6 days of life. Cost-effectiveness was primarily expressed in terms of incremental cost per additional case of adequate glucose control during the first 6 days of life. For the primary cost-effectiveness analysis, adequate glucose control was defined as at least 80% of readings falling within the target range. However, to assess the robustness of the cost-effectiveness results, a number of sensitivity analyses were also performed that varied the threshold for number of readings falling within the target range of 2.6–10 mmol/l. Therefore, adequate glucose control was re-estimated at alternative thresholds of 60%, 70% and 90% of readings falling within the target range. Given the nature of the outcome measure used in this project and the methodological constraints surrounding utility measurement in newborn infants, cost–utility analysis using a preference-based measure, such as quality-adjusted life-years, was not performed.

The secondary clinical outcome measures selected for secondary expressions of cost-effectiveness were NEC and BPD. Cost-effectiveness analyses using these secondary clinical outcome measures were expressed using the incremental cost-effectiveness ratio (ICER), and expressed in terms of incremental cost per case of NEC averted and incremental cost per case of BPD averted, using imputed costs for the entire period extending to 36 weeks' corrected gestation.

Cost-effectiveness analysis methods

Missing data
Missing data may be a particular issue for costs and the health outcome measures of interest; therefore, it is important to deal with them in a standardised way. RCTs have been criticised in the health economic literature for failing to use appropriate methods to address missing data.[51]

Multiple imputation was adopted to impute missing data and avoid biases associated with complete-case analysis. Multiple imputation was conducted based on Rubin's rule.[52] Multiple imputation was

carried out on the main and secondary clinical outcome measures, using Markov chain Monte Carlo and predicted mean matching.[53] Predicted mean matching is a semiparametric imputation approach and generally performs better than linear regression, despite the similarities in method.[54]

It is recommended that potential predictors are incorporated into analytical models for multiple imputation.[55] Inclusion of explanatory variables enables the analyst to use multivariate imputation through chained equations. In chained equations, missing values in variable X are replaced by draws from the posterior predictive distribution of X and imputation is repeatedly performed using the values of other independent variables.[55] Consequently, the multiple imputation models used baseline covariates (i.e. gestational age, sex, site and randomisation arm), as well as health outcomes and cost components (i.e. glucose level, and costs associated with inpatient days, investigation, medical treatment and surgical procedures).

For the CGM outcome, before implementing multiple imputation, linear interpolation using the known values of CGM, before and after any missing values, was conducted first, given that the data followed a time series format.[56] Interpolation requires that the dependent variable be a function of independent variables, so glucose level was also interpolated for values of the time that the glucose level was checked.[56,57] Then, likewise, the interpolated values were imputed using a chained equation with baseline covariates and costs. Five imputed data sets were generated, as this has been considered to be sufficient to obtain valid results.[53]

Regression analysis

Generalised linear modelling (GLM) was used to estimate total costs and effectiveness. GLM is an estimation strategy well suited to modelling skewed data.[58] Exponentiation of the mean of the logs generates the geometric mean of the skewed dependent variable (in this case, costs), which is a downwards-biased estimate of the arithmetic mean.[58] In contrast, GLM predicts the mean of the log without using a smearing factor and, therefore, tends to yield more consistent results. After conducting statistical tests, such as the Pregibon link test and Pearson correlation test, on cost data, the gamma family and log-link function were chosen as an appropriate generalised linear model for these trial data.

By specifying the treatment group as an indicator within the GLM, the incremental costs and outcomes attributable to CGM were estimated, while controlling for baseline covariates (i.e. treatment arm, study site, gestational age, sex, weight at birth, whether or not the mother received antenatal steroids > 24 hours prior to delivery, and whether or not the mother had diabetes during pregnancy).

Presentation of cost-effectiveness results

Summary statistics were estimated for resource use variables by treatment allocation and duration, covering either days 1–7 or the 36-week follow-up period. Between-group differences in resource use and costs were compared using the two-sample t-test. Standard errors (SEs) are reported for CGM and standard-care group means. Mean differences are reported with 95% CIs. When there was evidence of non-normality in the continuous outcome measure, non-parametric bootstrapping with 1000 samples was used to estimate the effect of the intervention and bootstrapped 95% CIs for mean differences are reported. Cost-effectiveness was estimated using a bootstrap method to minimise sampling uncertainty. Non-parametric bootstrap methods generate multiple replications of the statistic of interest by sampling replications from the original data.[58,59] A total of 1000 bootstrap samples were drawn and incremental effectiveness (with associated 95% CIs) was calculated. Estimates from each imputed data set were used to run regressions using Rubin's rule.[52]

To express uncertainty around ICERs and to display results across a range of cost-effectiveness thresholds, cost-effectiveness acceptability curves (CEACs) were generated on the basis of bootstrapped sample data.[60,61] These curves show the probability that CGM is cost-effective at different levels of the threshold based on modelled variation in observed patient outcomes.[62]

To determine cost-effectiveness, the use of CGMs was compared with standard care on the basis of the cost per additional case of adequate glucose control (ICER). An alternative that is less effective and more costly, on average, than one or a linear combination of other alternatives is considered 'dominated' in health economic terms and, therefore, it is not considered when estimating ICERs. An alternative that is more effective (i.e. provides the greatest additional adequate glucose control) and offers an ICER less than or equal to a benchmark value (the cost-effectiveness threshold) can be deemed 'cost-effective' compared with other alternatives.[62] However, there are currently no published cost-effectiveness thresholds for the primary and secondary clinical outcomes of the REACT trial. We searched the stated and revealed preference literature to identify any external evidence with respect to population preferences for health changes associated with adequate glucose control and for health changes associated with the secondary clinical outcomes, and no such preference values were revealed. Therefore, ranges of hypothetical cost-effectiveness threshold values have been selected for our analyses. As a result, the net monetary benefit (NMB) of CGM compared with standard care was calculated across three predetermined cost-effectiveness thresholds, namely £1000, £5000 and £10,000 per additional case of adequate glucose control.[63] Additionally, alternative cost-effectiveness threshold values were introduced for the secondary outcome analyses (£10,000, £30,000 and £50,000 cost-effectiveness thresholds). A positive incremental NMB indicates that the CGM is cost-effective compared with standard care at the given cost-effectiveness threshold.

Sensitivity and secondary outcomes analyses

Several sensitivity analyses were carried out to assess the robustness of the cost-effectiveness estimates. These were conducted under the following scenarios: (1) restricting the analyses to complete cases (i.e. those with complete cost and outcome data for the 7 days or up to 36 weeks' corrected gestation); and (2) estimating the incremental cost-effectiveness using different thresholds of 60%, 70% and 90% for adequate glucose control. The same sensitivity analyses described above were repeated over alternative follow-up periods of the first 7 days of life or extending to 36 weeks' corrected gestational age.

Two sets of prespecified subgroup analyses were conducted to explore the heterogeneity in the cost-effectiveness results. Subgroup analysis was performed for each study site and for two gestational age groups: extremely preterm (i.e. < 28 weeks' gestation) and very preterm (i.e. 28–32 weeks' gestation). A post hoc subgroup analysis was subsequently carried out using sex as an additional subgroup category. All subgroup analyses were based on cases with imputed cost and outcomes data at 7 days or 36 weeks' corrected gestational age.

Results of economic analysis

Table 35 in *Appendix 4* shows the completeness of health economic data by treatment allocation. The table shows that there were no missing data for resource use. Likewise, there were no missing data for the items such as use of the MiniMed 640G 3.0-ml insulin pump device, Guardian 2 Link and the Generation Enlite single sensor. Cases with data that were not available or not applicable are also reported if trial participants were withdrawn from the intervention and/or trial.

Health-care resource use

Table 16 shows resource use values for participants by trial group allocation and resource use category over the 7-day intervention period and the entire follow-up period for complete cases. The resource values are presented for subcategories of resource use, including hospital inpatient medications, investigation, medical treatment and surgical procedures. Use of Enlite sensors and glucose monitoring was reported for the 7-day intervention period only, as infants used the devices for this period only. Clinical recording of sensor glucose values was performed, on average, 121 times in infants in the CGM arm, but was not performed in infants in the standard-care arm, as the clinical team was masked to the sensor data.

TABLE 16 Randomised controlled trial: mean resource use by trial arm

Intervention period	Item	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 83), mean (SE)	Total (n = 154), mean (SE)
Days 1–7				
Enlite sensor (MiniMed system) (number of items)	MiniMed 640G 3.0-ml insulin pump	1.00 (0.00)	n/a	
	Guardian 2 Link	1.00 (0.00)	n/a	
	Generation Enlite single sensor: MMT-7008B	1.17 (0.04)	n/a	
Glucose monitoring (number of activities)	Glucose sensor insertion	1.17 (0.04)	n/a	
	Glucose sensor monitoring	121.14 (4.56)	n/a	
	Glucose sensor removal	1.17 (0.04)	n/a	
POC testing: used to calibrate the MiniMed 640G System (number of strips)	Nova Biomedical StatStrip meter	20.28 (1.05)	15.59 (0.91)	17.75 (0.71)
Length of stay (days)	Intensive care	6.01 (0.23)	5.95 (0.23)	5.98 (0.16)
	High-dependency care	0.96 (0.23)	0.87 (0.21)	0.91 (0.15)
	Special care	0.01 (0.01)	0.08 (0.08)	0.05 (0.05)
	Transitional care	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Medications (days of use during intervention period)	Inotropes	0.59 (0.17)	0.69 (0.17)	0.64 (0.12)
	Antibiotics	4.61 (0.29)	4.48 (0.24)	4.54 (0.18)
	Caffeine	6.73 (0.13)	6.69 (0.11)	6.71 (0.09)
	Morphine	1.77 (0.31)	1.67 (0.27)	1.72 (0.20)
	Corticosteroids	0.04 (0.03)	0.06 (0.04)	0.05 (0.02)
Insulin (ml/kg)	Insulin	0.02 (0.00)	0.01 (0.00)	0.01 (0.00)
Investigations (number of items)	Cranial ultrasound	2.25 (0.12)	2.27 (0.12)	2.26 (0.08)
	Other ultrasound	0.01 (0.01)	0.04 (0.02)	0.03 (0.01)
	CT	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	X-ray	3.79 (0.27)	4.34 (0.29)	4.08 (0.20)
	EEG	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	MRI	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Echocardiography	0.58 (0.12)	0.63 (0.09)	0.60 (0.07)
	ECG	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Blood transfusion products (number of products)	Platelets	0.15 (0.06)	0.14 (0.05)	0.15 (0.04)
	Red blood cells	0.63 (0.12)	0.76 (0.13)	0.70 (0.09)
	Fresh-frozen plasma	0.08 (0.04)	0.07 (0.03)	0.08 (0.02)
Medical treatment (number of treatments)	Lumbar punctures	0.11 (0.04)	0.11 (0.04)	0.11 (0.03)
	Ventricular taps	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Long lines	0.93 (0.07)	0.90 (0.09)	0.92 (0.06)

TABLE 16 Randomised controlled trial: mean resource use by trial arm (*continued*)

Intervention period	Item	CGM arm (*n* = 71), mean (SE)	Standard-care arm (*n* = 83), mean (SE)	Total (*n* = 154), mean (SE)
Surgical procedures (number of procedures)	Ventriculoperitoneal shunts	0.01 (0.01)	0.00 (0.00)	0.01 (0.01)
	Surgical procedures for central access	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
	Interventions for ROP treatment	0.01 (0.01)	0.00 (0.00)	0.01 (0.01)
Other procedures		0.00 (0.00)	0.06 (0.03)	0.03 (0.02)
		n = 71	*n* = 82	*n* = 153
Day 8 to 36 weeks' corrected gestation				
Length of stay (days)	Intensive care	13.15 (1.64)	16.71 (1.83)	15.06 (1.24)
	High-dependency care	25.06 (2.00)	24.8 (1.51)	24.92 (1.23)
	Special care	16.55 (1.68)	15 (1.51)	15.72 (1.12)
	Transitional care	0.44 (0.25)	0.22 (0.11)	0.32 (0.13)
Medication (ml)	Insulin (ml/g)	0.004 (0.00)	0.003 (0.00)	0.00 (0.00)
Investigations (number of items)	Cranial ultrasound	2.87 (0.29)	3.02 (0.20)	2.95 (0.17)
	Other ultrasound	0.17 (0.08)	0.38 (0.20)	0.28 (0.11)
	CT	0 (0.00)	0.01 (0.01)	0.01 (0.01)
	X-ray	3.87 (0.58)	4.93 (0.65)	4.44 (0.44)
	EEG	0 (0.00)	0.01 (0.01)	0.01 (0.01)
	MRI	0.01 (0.01)	0.05 (0.02)	0.03 (0.01)
	Echocardiography	0.96 (0.17)	1.18 (0.17)	1.08 (0.12)
	ECG	0.04 (0.02)	0 (0.00)	0.02 (0.01)
Blood transfusion products (number of products)	Platelets	0.07 (0.03)	0.04 (0.02)	0.05 (0.02)
	Red blood cells	1.75 (0.25)	2.23 (0.30)	2.01 (0.20)
	Fresh-frozen plasma	0.11 (0.05)	0.11 (0.05)	0.11 (0.04)
Medical treatment (number of treatments)	Lumbar punctures	0.1 (0.04)	0.23 (0.06)	0.17 (0.04)
	Ventricular taps	0.27 (0.07)	0.5 (0.13)	0.39 (0.08)
	Long lines	0 (0.00)	0.04 (0.03)	0.02 (0.01)
Surgical procedures (number of procedures)	Ventriculoperitoneal shunts	0.03 (0.02)	0.05 (0.02)	0.04 (0.02)
	Surgical procedures for central access	0 (0.00)	0.02 (0.02)	0.01 (0.01)
	Interventions for ROP treatment	0 (0.00)	0.01 (0.01)	0.01 (0.01)
Other procedures		0.01 (0.01)	0.07 (0.03)	0.05 (0.02)
Transfers to other hospital (number by mode)	Air ambulance transfers	0 (0.00)	0.02 (0.02)	0.01 (0.01)
	Road transfers	0.49 (0.06)	0.43 (0.05)	0.46 (0.04)

n/a, not applicable.

Economic costs

Table 17 summarises the total NHS and PSS costs associated with resource use during days 1–7, day 8 to 36 weeks' corrected gestational age and the entire study period for complete cases. *Table 18* breaks these costs down by subcategory. The mean direct intervention costs over the first 7 days were £11,198 in the CGM arm and £9934 for the standard-care arm; the mean difference was not statistically significant at the 5% level. The cost of using the Enlite sensor and glucose monitoring was not included in the standard-care arm, as it is not part of standard care. The total cost during the period covering day 8 to 36 weeks' corrected gestational age was higher in the standard-care arm (£61,065 vs. £65,464), but the difference was not statistically significant at the 5% level. The main driver for the higher cost in the standard-care arm during the follow-up period was the higher cost of neonatal care. Likewise, the mean total NHS and PSS cost throughout the entire follow-up period was higher in the standard-care group (£75,348) than in the CGM group (£71,909), but the mean between-group cost difference of –£3439 was not statistically significant at the 5% level.

Cost-effectiveness results

The cost-effectiveness results are presented in *Tables 19* and *20* for days 1–7 and the entire study period, respectively. The associated CEACs and cost-effectiveness scatterplots are graphically represented in *Figures 16–19*.

Base-case analysis

Two base-case analyses were performed. The first was imputed 7-day intervention costs and cases of adequate glucose control (see *Table 19*), with an 80% threshold selected for definition of adequate glucose control. The second was imputed costs and cases of adequate glucose control (80% threshold), but with costs extending to 36 weeks' corrected gestational age and outcomes restricted to the intervention period (see *Table 20*). For the first base-case analysis, trial participants in the CGM arm experienced a statistically significant increase in cases of adequate glucose control based on 1000 bootstrap simulations (i.e. a 23 percentage-point increase in the rate of adequate glucose control) during the first 7 days. The mean NHS and PSS costs (see *Table 19*) were also lower in the standard-care group (mean cost difference £605). The ICER for the base-case analysis in *Table 19* indicates that using CGM is, on average, more costly and more effective than standard care. Assuming cost-effectiveness thresholds of £1000, £5000 and £10,000 per additional case of adequate glucose control, the probability of cost-effectiveness for CGM reaches 90% at approximately £6000 (see *Figure 16*), whereas the NMB associated with use of a CGM became positive at a cost-effectiveness threshold of £5000 (see *Table 19*).

For the second base-case analysis (see *Table 20*), the trial participants in the CGM arm experienced lower costs (mean cost difference –£2877) and a 23 percentage-point increase in cases of adequate glucose control, as before. CGM was not only less costly, but also the more effective strategy in this second base-case analysis and, therefore, dominant in health economic terms. To summarise, the base-case analyses reported in *Table 20* show that CGM is the dominant strategy in health economics terms.

Sensitivity analyses

It was found that the cost-effectiveness results from the sensitivity analyses using different analytical scenarios (i.e. complete case and imputed costs with 60%, 70% and 90% thresholds selected for definitions of additional adequate glucose control) generally supported the base-case findings. In the complete-case analysis (see *Table 19*), mean costs were higher in the CGM arm (mean cost difference £1104, 95% CI –£38.56 to £2247.11) than in the standard-care arm. The effectiveness results followed the same pattern as that of the base-case analysis and showed that participants in the CGM arm experienced a statistically significant increase in the proportion of glucose readings within the target range over the 7-day intervention period (0.22, 95% CI 0.05 to 0.4). For the four sets of sensitivity analyses (see *Table 19*), the probabilities of cost-effectiveness of using CGM reach approximately 90% at cost-effectiveness thresholds of £10,000. Adopting 60%, 70% and 90% thresholds for proportions of glucose readings within the target ranges, the costs for each group

TABLE 17 Randomised controlled trial: cost (£) differences between trial arms by follow-up period and cost category

Cost	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 83), mean (SE)	Total (n = 154), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Days 1–7							
Equipment	87 (2)	n/a	n/a	n/a	n/a	n/a	n/a
Monitoring	165 (6)	n/a	n/a	n/a	n/a	n/a	n/a
POC testing	6 (0.3)	5 (0.3)	5 (0.2)	1.4	0.6 to 2.2	0.001	0.6 to 2.2
Length of stay	8656 (97)	8534 (132)	8590 (84)	121	−213 to 455	0.5	−172 to 482
Medications	79 (2)	77 (1)	78 (1)	−2.8	−2.8 to 5.3	0.5	−3.3 to 4.9
Investigation	571 (31)	630 (33)	603 (23)	−59	−148 to 31	0.2	−148 to 32
Blood transfusion products	2 (2)	35.7 (34)	20 (19)	−14	−63 to 35	0.4	−68 to 35
Medical treatment	92 (17)	106 (18)	100 (12)	17	−153 to 186	0.6	−139 to 196
Surgical procedures	544 (57)	527 (62)	535 (43)	−34	−108 to 39	0.8	−132 to 2
Other procedures	2 (2)	36 (34)	20 (19)	−34	−108 to 39	0.4	−144 to 3
Total	11,199 (976)	9934 (184)	10,517 (462)	1265	68 to 4168	0.2	−560 to 3090

Cost	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 82), mean (SE)	Total (n = 153), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Day 8 to 36 weeks' corrected gestational age							
Length of stay	59,901 (2296)	62,807 (2059)	61,458 (1533)	−2906	−8983 to 3170	0.3	−9020 to 2400
Medication: insulin only	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1	−0.1 to 0.4	0.2	−0.1 to 0.4
Investigation	677 (76)	841 (97)	765 (63)	−165	−414 to 84	0.2	−443 to 53
Blood transfusion products	222 (34)	279 (39)	252 (26)	−57	−161 to 47	0.3	−157 to 52
Medical treatment	244 (64)	531 (105)	398 (65)	−287	−540 to −35	0.03	−535 to −65
Surgical procedures	20 (14)	909 (837)	496 (449)	−889	−2667 to 889	0.3	−3289 to −21
Other procedures	0 (0)	94 (62)	50 (33)	−94	−225 to 38	0.2	−244 to −5
Mode of transfers	2.8 (0.4)	3.6 (1)	3.2 (0.6)	−0.8	−3.1 to 1.4	0.5	−3.3 to 0.8
Total	61,065 (2376)	65,464 (2381)	63,423 (1690)	−4399	−11,080 to 2283	0.2	−10,713 to 1773

TABLE 17 Randomised controlled trial: cost (£) differences between trial arms by follow-up period and cost category (*continued*)

Cost	CGM arm (n = 69), mean (SE)	Standard-care arm (n = 81), mean (SE)	Total (n = 150), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Entire study period							
Equipment	87 (2)	n/a	n/a	n/a	n/a	n/a	n/a
Monitoring	165 (6)	n/a	n/a	n/a	n/a	n/a	n/a
POC testing	5.8 (0.3)	4.5 (0.3)	5.1 (0.2)	1.3	0.5 to 2.1	0.002	0.6 to 2.2
Length of stay	68,144 (2563)	71,273 (2101)	69,833 (1636)	−3129	−9616 to 3358	0.3	−9577 to 3043
Medications	79 (2)	78 (1)	78 (1)	−2.7	−2.7 to 5.5	0.5	−3 to 5.5
Investigation	1260 (94)	1471 (115)	1374 (76)	−212	−513 to 89	0.2	−505 to 88
Blood transfusion products	320 (49)	387 (53)	356 (36)	−67	−211 to 78	0.4	−203 to 71
Medical treatment	798 (99)	1062 (131)	941 (85)	−264	−598 to 70	0.1	−587 to 45
Surgical procedures	1047 (994)	939 (848)	989 (645)	109	−2457 to 2674	0.9	−2313 to 3007
Other procedures	2 (2)	131 (72)	72 (39)	−130	−284 to 25	0.1	−294 to −7
Mode of transfers	2.8 (0.4)	3.6 (1)	3.3 (0.6)	−0.8	−3.1 to 1.5	0.5	−3.2 to 1
Total	71,910 (2779)	75,348 (2476)	73,767 (1849)	−3439	−10,645 to 2939	0.4	−10,774 to 3896

n/a, not applicable.
Reprinted from *Seminars in Perinatology*, vol. 45, Petrou S, Kim S, Bond S, Allison A, Beardsall K, the REACT collaborative, Cost-effectiveness of real time continuous glucose monitoring to target glucose control in preterm infants, pp. 151392, Copyright (2021),[43] with permission from Elsevier.

TABLE 18 Randomised controlled trial: cost (£) differences between trial arms

Cost	Item	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 83), mean (SE)	Total (n = 154), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Days 1–7								
Enlite sensor (MiniMed System) (item)	MiniMed 640G	14 (0)	n/a	n/a	n/a	n/a	n/a	n/a
	Guardian 2 Link	9 (0)	n/a	n/a	n/a	n/a	n/a	n/a
	Generation Enlite single sensor: MMT-7008B	64 (2.4)	n/a	n/a	n/a	n/a	n/a	n/a
Glucose monitoring	Enlite sensor insertion	6 (0.2)	n/a	n/a	n/a	n/a	n/a	n/a
	Enlite sensor monitoring	157 (6)	n/a	n/a	n/a	n/a	n/a	n/a
	Enlite sensor removal	2.5 (0.1)	n/a	n/a	n/a	n/a	n/a	n/a
POC testing	Nova Biomedical StatStrip meter for calibration of 640G device	5.9 (0.3)	4.5 (0.3)	5.1 (0.2)	1.4	0.6 to 2.2	0.001	0.6 to 2.1
Length of stay	Intensive care	7788 (304)	7708 (297)	7745 (212)	81	–762 to 923	0.9	–720 to 810
	High-dependency care	859 (205)	778 (188)	816 (138)	81	–467 to 629	0.8	–416 to 648
	Special care	8 (8)	49 (49)	30 (27)	–41	–146 to 65	0.4	–167 to 17
	Transitional care	0 (0)	0 (0)	0 (0)	0			
Medications	Inotropes	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0	–0.1 to 0	0.7	–0.1 to 0.1
	Antibiotics	3.5 (0.2)	3.4 (0.2)	3.4 (0.1)	0.1	–0.5 to 0.6	0.7	–0.5 to 0.6
	Caffeine	74 (1.5)	73 (1.2)	74 (0.9)	0.5	–3.3 to 4.3	0.8	–3.4 to 4.1
	Morphine	0 (0)	0 (0)	0 (0)	0	0 to 0	0.8	0 to 0.0
	Corticosteroids	0 (0)	0 (0)	0 (0)	0	0 to 0	0.7	0 to 0.0
	Insulin	1.1 (0.2)	0.5 (0.1)	0.8 (0.1)	0.6	0.2 to 1.2	0.007	0.2 to 1.1

TABLE 18 Randomised controlled trial: cost (£) differences between trial arms (continued)

Cost	Item	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 83), mean (SE)	Total (n = 154), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Investigations	Cranial ultrasound	159 (9)	160 (8)	160 (6)	−0.8	−25 to 23	0.9	−27 to 23
	Other ultrasound	1 (1)	2.6 (1.5)	1.8 (0.9)	−1.6	−5 to 2	0.4	−4.9 to 2.1
	CT	0 (0)	0 (0)	0 (0)	0			
	X-rays	360 (25)	412 (27)	388 (19)	−52	−127 to 22	0.2	−121 to 25
	EEG	0 (0)	0 (0)	0 (0)	0			
	MRI	0 (0)	0 (0)	0 (0)	0			
	Echocardiography	51 (10)	55 (8)	53 (6)	−4	−30 to 21	0.7	−30 to 22
	ECG	0 (0)	0 (0)	0 (0)	0			
Blood transfusion products	Platelets	14 (5)	13 (4)	14 (3)	0.9	−13 to 14	0.9	−12 to 14
	Red blood cells	76 (14)	91 (15)	84 (10)	−15	−56 to 26	0.5	−52 to 28
	Fresh-frozen plasma	2.4 (1.1)	2.1 (0.8)	2.2 (0.7)	0.3	−2.3 to 3	0.8	−2 to 3.4
Medical (surgical) treatments	Lumbar puncture	148 (50)	143 (51)	145 (36)	6	−136 to 147	0.9	−137 to 149
	Ventricular tap	0 (0)	0 (0)	0 (0)	0			
	Long line	396 (30)	385 (40)	390 (25)	11	−89 to 111	0.8	−93 to 92
Surgical procedures	Interventions for ROP treatment	10 (10)	0 (0)	4.5 (4.5)	10	−8 to 28	0.3	0 to 36
	Surgical procedures for central access	22 (22)	19 (19)	20 (14)	3	−53 to 59	0.9	−51 to 65
	Ventriculoperitoneal shunts	967 (967)	0 (0)	446 (446)	967	−799 to 2732	0.3	0 to 3550
Other procedures		1.5 (1.5)	36 (34)	20 (19)	−34	−108 to 39	0.4	−144 to 2.6
Total costs		11,199 (976)	9934 (184)	10,517 (462)	1265	68 to 4168	0.2	−560 to 3090

Cost	Item	CGM arm (*n* = 71), mean (SE)	Standard-care arm (*n* = 82), mean (SE)	Total (*n* = 153), mean (SE)	Mean difference	Parametric 95% CI	*p*-value	Bootstrapped 95% CI
Day 8 to 36 weeks' corrected gestational age								
Length of stay	Intensive care	17,036 (2119)	21,636 (2368)	19,501 (1611)	−4600	−10,962 to 1762	0.2	−10,885 to 1774
	High-dependency care	22,476 (1791)	22,250 (1352)	22,355 (1099)	226	−4143 to 4594	0.9	−3824 to 4645
	Special care	9549 (970)	8655 (874)	9070 (648)	894	−1679 to 3467	0.5	−1649 to 3617
	Transitional care	10,840 (1160)	10,266 (1037)	10,533 (772)	575	−2491 to 3640	0.7	−2274 to 3952
Medications	Insulin	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)	0.1	−0.1 to 0.4	0.2	−0.1 to 0.4
Investigations	Cranial ultrasound	203 (21)	214 (14)	209 (12)	−11	−59 to 38	0.7	−58 to 38
	Other ultrasound	12 (6)	27 (14)	20 (8)	−15	−46 to 17	0.4	−48 to 12
	CT	0 (0)	1.4 (1.4)	0.8 (0.8)	−1.4	−4.4 to 1.6	0.4	−6.1 to 0
	X-ray	368 (56)	468 (61)	422 (42)	−100	−266 to 66	0.2	−256 to 66
	EEG	0 (0)	15 (15)	8.2 (8.2)	−15	−48 to 17	0.4	−58 to 0
	MRI	3.3 (3.3)	11 (6)	7.6 (3.4)	−8	−21 to 5.2	0.2	−22 to 3.9
	Echocardiography	85 (15)	104 (15)	95 (11)	−20	−62 to 23	0.4	−60 to 24
	ECG	5.6 (3.2)	0 (0)	2.6 (1.5)	5.6	−0.3 to 12	0.06	0 to 14
Blood transfusion products	Platelets	10 (4.6)	9.9 (4.7)	10 (3.3)	0.3	−13 to 13	1.0	−14 to 13
	Red blood cells	210 (31)	268 (36)	241 (24)	−58	−154 to 37	0.2	−164 to 31
	Fresh-frozen plasma	2 (0.9)	1 (0.6)	1.5 (0.5)	1	−1.1 to 3	0.4	−1 to 3.3
Medical (surgical) treatments	Lumbar puncture	130 (47)	305 (80)	224 (49)	−175	−366 to 16	0.07	−380 to −11
	Ventricular tap	114 (32)	213 (55)	167 (33)	−99	−230 to 33	0.1	−246 to 3.8
	Long line	0 (0)	13 (9.7)	7 (5.2)	−13	−34 to 7.6	0.2	−38 to 0

TABLE 18 Randomised controlled trial: cost (£) differences between trial arms (*continued*)

Cost	Item	CGM arm (n = 71), mean (SE)	Standard-care arm (n = 82), mean (SE)	Total (n = 153), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Surgical procedures	Interventions for ROP treatment	20 (14)	34 (17)	27 (11)	−14	−58 to 29	0.5	−60 to 28
	Surgical procedures for central access	0 (0)	38 (26)	20 (14)	−38	−93 to 19	0.2	−106 to 0
	Ventriculoperitoneal shunts	0 (0)	837 (837)	449 (449)	−837	−2615 to 941	0.4	−3566 to 0
Other procedures		0 (0)	93.7 (62)	50 (33)	−94	−225 to 38	0.2	−241 to −5.3
Mode of transfers	Air ambulance	0 (0)	0.9 (0.6)	0.5 (0.3)	−0.9	−2.5 to 0	0.2	−2.2 to 0.5
	Road	2.8 (0.4)	2.7 (0.5)	2.7 (0.3)	0.1	−1.3 to 1.5	0.9	−1.2 to 1.5
Total		61,065 (2376)	65,464 (2381)	63,423 (1690)	−4399	−11,080 to 2283	0.2	−10,972 to 2187

Cost	Item	CGM arm (n = 69), mean (SE)	Standard-care arm (n = 81), mean (SE)	Total (n = 150), mean (SE)	Mean difference	Parametric 95% CI	p-value	Bootstrapped 95% CI
Entire study period								
Enlite sensor (MiniMed System)	MiniMed 640G System	14 (0)	n/a	n/a	n/a	n/a	n/a	n/a
	Guardian 2 Link	9 (0)	n/a	n/a	n/a	n/a	n/a	n/a
	Generation Enlite single sensor MMT-7008B	64 (2.4)	n/a	n/a	n/a	n/a	n/a	n/a
Glucose monitoring	Enlite sensor insertion	6.1 (0.2)	n/a	n/a	n/a	n/a	n/a	n/a
	Enlite sensor monitoring	157 (6)	n/a	n/a	n/a	n/a	n/a	n/a
	Enlite sensor removal	2.5 (0.1)	n/a	n/a	n/a	n/a	n/a	n/a
POC testing	Nova Biomedical StatStrip meter for calibration of 640G device	5.8 (0.3)	4.5 (0.3)	5.1 (0.2)	1.3	0.5 to 2.1	0.002	0.5 to 2
Length of stay (days)	Intensive care	25,149 (2273)	29,433 (2480)	27,463 (1702)	−4284	−11,021 to 2452	0.2	−11,182 to 1828
	High-dependency care	23,439 (1782)	22,946 (1339)	23,173 (1089)	494	−3839 to 4826	0.8	−3381 to 4696
	Special care	8973 (998)	8669 (890)	8809 (662)	304	−2331 to 2938	0.8	−2138 to 2963
	Transitional care	10,583 (1177)	10,225 (1049)	10,389 (781)	358	−2749 to 3465	0.8	−2679 to 3392

Cost	Item	CGM arm (*n* = 69), mean (SE)	Standard-care arm (*n* = 81), mean (SE)	Total (*n* = 150), mean (SE)	Mean difference	Parametric 95% CI	*p*-value	Bootstrapped 95% CI
Medications	Inotropes	0.1 (0)	0.1 (0)	0.1 (0)	0	−0.1 to 0.1	0.7	−0.1 to 0.1
	Antibiotics	3.5 (0.2)	3.4 (0.2)	3.4 (0.1)	0.1	−0.5 to 0.6	0.8	−0.5 to 0.7
	Caffeine	74 (1.5)	73 (1.3)	74 (1)	0.5	−3.4 to 4.4	0.8	−4.2 to 4
	Morphine	0 (0)	0 (0)	0 (0)	0	0 to 0	0.9	0 to 0
	Corticosteroids	0 (0)	0 (0)	0 (0)	0	0 to 0	0.7	0 to 0
	Insulin	1.5 (0.3)	0.6 (0.1)	1 (0.2)	0.8	0.2 to 1.6	0.01	0.2 to 1.5
Investigations	Cranial ultrasound	365 (24)	375 (19)	370 (15)	−9.7	−70 to 50	0.8	−65 to 58
	Other ultrasound	13 (6.2)	30 (15)	22 (8.5)	−16	−50 to 17	0.3	−57 to 8.3
	CT	0 (0)	1.4 (1.4)	0.8 (0.8)	−1.4	−4.5 to 1.6	0.4	−5 to 0
	X-ray	734 (67)	877 (79)	811 (53)	−143	−352 to 65	0.2	−336 to 55
	EEG	0 (0)	16 (16)	8.4 (8.4)	−16	−49 to 18	0.4	−53 to 0
	MRI	3.4 (3.4)	12 (5.6)	7.7 (3.4)	−8.1	−22 to 5.4	0.2	−21 to 3.7
	Echocardiography	138 (21)	161 (20)	151 (15)	−23	−81 to 35	0.4	−81 to 33
	ECG	5.8 (3.3)	0 (0)	2.7 (1.5)	5.8	−0.2 to 12	0.06	1.8 to 14
Blood transfusion products	Platelets	258 (8.7)	23 (7.9)	24 (5.8)	1.5	−22 to 25	0.9	−20 to 25
	Red blood cells	290 (42)	360 (48)	328 (32)	−70	−198 to 58	0.3	−203 to 47
	Fresh-frozen plasma	4.5 (1.4)	3.2 (1)	3.8 (0.8)	1.4	−1.9 to 4.7	0.4	−1.6 to 5.4
Medical (surgical) treatments	Lumbar puncture	286 (76)	455 (104)	377 (66)	−169	−431 to 93	0.2	−432 to 74
	Long line	512 (50)	594 (72)	556 (45)	−82	−262 to 98	0.4	−266 to 64
	Ventricular tap	0 (0)	13 (9.9)	7.2 (5.3)	−13	−34 to 7.8	0.2	−38 to 0

TABLE 18 Randomised controlled trial: cost (£) differences between trial arms (*continued*)

Cost	Item	CGM arm (*n* = 69), mean (SE)	Standard-care arm (*n* = 81), mean (SE)	Total (*n* = 150), mean (SE)	Mean difference	Parametric 95% CI	*p*-value	Bootstrapped 95% CI
Surgical procedures	Interventions for ROP treatment	30 (17)	35 (17)	33 (12)	−4	−52 to 44	0.9	−54 to 42
	Surgical procedures for central access	22 (22)	57 (42)	41 (25)	−35	−134 to 64	0.5	−143 to 47
	Ventriculoperitoneal shunts	995 (995)	847 (847)	915 (645)	147	−2418 to 2713	0.9	−1716 to 3269
Other procedures		1.5 (1.5)	131 (72)	72 (39)	−130	−284 to 25	0.10	−319 to −8.4
Mode of transfers	Air ambulance	0 (0)	0.9 (0.6)	0.5 (0.3)	−0.9	−2.2 to 0.4	0.2	−2.6 to 0
	Road	2.8 (0.4)	2.8 (0.5)	2.8 (0.3)	0.1	−1.3 to 1.5	0.9	−1.5 to 1.4
Total costs		71,910 (2779)	75,348 (2476)	73,766.5 (1849)	−3439	−10,645 to 2939	0.4	−10,774 to 3896

n/a, not applicable.

Note
Data presented by follow-up period and resource category for participants with complete data (2017 prices).
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TABLE 19 Randomised controlled trial: results of cost-effectiveness analyses (days 1–7)

| Scenario | Trial arm, mean (SE) cost (£) | | Incremental cost (£) (95% CI) | Trial arm, mean (SE) cost (£) | | Incremental effectiveness (95% CI) | ICER | Probability of cost-effectiveness at threshold | | | NMB (£) at threshold | | |
	CGM	Standard care		CGM	Standard care			£1000	£5000	£10,000	£1000 (95% CI)	£5000 (95% CI)	£10,000 (95% CI)
Base-case analysis													
Imputed costs and cases of adequate glucose control (80% threshold), covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.92 (0.05)	0.68 (0.05)	0.23 (0.07 to 0.4)	2583	0.31	0.86	0.97	–276 (–308 to –245)	718 (677 to 759)	1961 (1899 to 2023)
Sensitivity analyses													
Complete-case attributable costs and cases of adequate glucose control (80% threshold)	11,117 (743)	10,013 (370)	1104 (–39 to 2247)	0.93 (0.05)	0.7 (0.06)	0.22 (0.05 to 0.4)	4923	0.08	0.56	0.89	–827 (–864 to –790)	138 (90 to 185)	1344 (1276 to 1413)
Imputed costs and cases of adequate glucose control (90% threshold), covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.80 (0.1)	0.58 (0.06)	0.23 (–0.03 to 0.48)	2670	0.33	0.81	0.93	–266 (–376 to –157)	752 (581 to 923)	2025 (1740 to 2309)
Imputed costs and cases of adequate glucose control (70% threshold), covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.97 (0.04)	0.75 (0.05)	0.21 (0.06 to 0.36)	2870	0.27	0.85	0.97	–292 (–396 to –189)	621 (499 to 742)	1762 (1590 to 1935)
Imputed costs and cases of adequate glucose control (60% threshold), covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.97 (0.03)	0.83 (0.04)	0.14 (0.04 to 0.25)	4223	0.26	0.65	0.90	–370 (–475 to –265)	233 (114 to 352)	987 (835 to 1139)
Subgroup analysis[a] **Stratification by centre**													
Cambridge N01	12,542 (2275)	9873 (357)	2670 (–1819 to 7158)	0.88 (0.06)	0.63 (0.1)	0.26 (0.03 to 0.48)	10,469	0.17	0.19	0.27	–2444 (–3015 to –1874)	–2251 (–2821 to –1681)	–2009 (–2582 to –1437)
Norwich N42	7770 (1163)	10,297 (251)	–2527 (–4871 to –182)	1	0.86 (0.12)	0.14 (–0.09 to 0.37)	–17,686	0.96	0.98	0.99	3666 (3345 to 3987)	4087 (3753 to 4420)	4612 (4251 to 4973)
Luton and Dunstable N43	10,622 (182)	9309 (686)	1312 (–88 to 2714)	0.91 (0.08)	0.69 (0.13)	0.22 (–0.06 to 0.49)	6056	0.19	0.28	0.49	–982 (–1196 to –768)	–495 (–704 to –285)	114 (–108 to 336)

TABLE 19 Randomised controlled trial: results of cost-effectiveness analyses (days 1–7) (*continued*)

Scenario	Trial arm, mean (SE) cost (£)		Incremental cost (£) (95% CI)	Trial arm, mean (SE) cost (£)		Incremental effectiveness (95% CI)	ICER	Probability of cost-effectiveness at threshold			NMB (£) at threshold		
	CGM	Standard care		CGM	Standard care			£1000	£5000	£10,000	£1000 (95% CI)	£5000 (95% CI)	£10,000 (95% CI)
Wolverhampton N68	9592 (383)	9470 (788)	122 (–1517 to 1760)	0.82 (0.12)	0.69 (0.15)	0.13 (–0.26 to 0.51)	968	0.36	0.53	0.62	–317 (–498 to –136)	21 (–192 to 234)	444 (179 to 708)
Southampton N73	9181 (889)	8112 (546)	1069 (–1169 to 3307)	1	0.83 (0.1)	0.17 (–0.04 to 0.37)	6413	0.63	0.71	0.87	824 (291 to 1357)	1582 (1128 to 2036)	2529 (2100 to 2958)
Amsterdam ND3	10,282 (535)	9290 (853)	992 (–848 to 2832)	1 (0)	0.75 (0.17)	0.25 (–0.08 to 0.58)	3967	0.40	0.56	0.72	–758 (–859 to –658)	–462 (–583 to –341)	–92 (–302 to 118)
Stratification by gestational age at birth													
Extremely preterm (< 28 weeks' gestation)	10,035 (292)	10,018 (254)	17 (–820 to 854)	0.88 (0.06)	0.64 (0.06)	0.24 (0.08 to 0.4)	71	0.69	0.99	1	221 (133 to 310)	1191 (1067 to 1315)	2403 (2212 to 2594)
Very preterm (28–32 weeks' gestation)	11,531 (1724)	8937 (370)	2594 (–785 to 5972)	0.93 (0.05)	0.79 (0.08)	0.14 (–0.05 to 0.33)	18,501	0.03	0.16	0.29	–2541 (–2886 to –2196)	–1947 (–2305 to –1589)	–1204 (–1601 to –807)
Stratification by sex													
Male	9539 (331)	9735 (299)	–196 (–1041 to 650)	0.91 (0.05)	0.60 (0.08)	0.31 (0.12 to 0.5)	–632	0.88	1	1	498 (410 to 585)	1734 (1608 to 1859)	3278 (3074 to 3483)
Female	11,666 (1595)	9517 (269)	2150 (–1037 to 5336)	0.88 (0.06)	0.78 (0.07)	0.10 (–0.07 to 0.27)	21,496	0.08	0.22	0.27	–2077 (–2400 to –1753)	–1678 (–2010 to –1346)	–1179 (–1540 to –819)
								£10,000	£30,000	£50,000	£10,000 (95% CI)	£30,000 (95% CI)	£50,000 (95% CI)
Secondary analysis													
Imputed costs and cases of BPD averted, covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.66 (0.17)	0.52 (0.12)	0.14 (–0.28 to 0.56)	4286	0.65	0.73	0.74	962 (819 to 1105)	3936 (3531 to 4342)	6910 (6240 to 7580)
Imputed costs and cases of NEC averted, covariate adjusted	10,354 (597)	9749 (282)	605 (–379 to 1589)	0.87 (0.05)	0.71 (0.06)	0.16 (0 to 0.33)	3697	0.82	0.95	0.97	1085 (885 to 1285)	4296 (3781 to 4812)	7508 (6662 to 8354)

a Subgroup analysis by site could not be performed for Oxford (N36), Surrey (N74), Barts (N85), Bristol (N86), Leeds (N87), Leicester (N88) or Barcelona (SP3) because of insufficient number of observations.
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TABLE 20 Randomised controlled trial: results of the cost-effectiveness analyses (day 1 to 36 weeks' corrected gestational age)

Scenario	Trial arm, mean (SE) cost (£)			Trial arm, mean (SE) cost (£)				Probability of cost-effectiveness at threshold			NMB (£) at threshold		
	CGM	Standard care	Incremental cost (£) (95% CI)	CGM	Standard care	Incremental effectiveness (95% CI)	ICER	£1000	£5000	£10,000	£1000 (95% CI)	£5000 (95% CI)	£10,000 (95% CI)
Base-case analysis													
Imputed costs and cases of adequate glucose control (80% threshold), covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.92 (0.05)	0.68 (0.05)	0.23 (0.07 to 0.4)	−12,273	0.8	0.86	0.92	3227 (3000 to 3454)	4221 (3990 to 4452)	5464 (5225 to 5703)
Sensitivity analyses													
Complete-case attributable costs and cases of adequate glucose control (80% threshold)	73,200 (2480)	74,773 (2237)	−1574 (−6557 to 3410)	0.93 (0.05)	0.7 (0.06)	0.22 (0.05 to 0.4)	−7016	0.07	0.62	0.91	1802 (1643 to 1961)	2768 (2602 to 2933)	3974 (3797 to 4151)
Imputed costs and cases of adequate glucose control (90% threshold), covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.8 (0.1)	0.58 (0.06)	0.23 (−0.03 to 0.48)	−12,687	0.81	0.86	0.91	3375 (2593 to 4156)	4393 (3576 to 5210)	5666 (4789 to 6542)
Imputed costs and cases of adequate glucose control (70% threshold), covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.97 (0.04)	0.75 (0.05)	0.21 (0.06 to 0.36)	−13,637	0.81	0.85	0.9	3348 (2572 to 4124)	4262 (3476 to 5047)	5403 (4599 to 6207)
Imputed costs and cases of adequate glucose control (60% threshold), covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.97 (0.03)	0.83 (0.04)	0.14 (0.04 to 0.25)	−20,066	0.81	0.83	0.89	3271 (2494 to 4048)	3874 (3085 to 4663)	4628 (3820 to 5436)
Subgroup analysis[a]													
Stratification by centre													
Cambridge N01	82,336 (2895)	79,688 (4287)	2648 (−7706 to 13,002)	0.88 (0.06)	0.63 (0.1)	0.26 (0.03 to 0.48)	10,385	0.3	0.38	0.56	−1997 (−3043 to −951)	−963 (−2006 to 81)	330 (−722 to 1381)
Norwich N42	63,545 (19515)	73,956 (4990)	−10,411 (−48,985 to 28,162)	1	0.86 (0.12)	0.14 (−0.09 to 0.37)	−72,879	0.79	0.79	0.82	12,753 (8126 to 17,379)	13,695 (9059 to 18,331)	14,874 (10,222 to 19,525)
Luton and Dunstable N43	70,091 (6103)	74,115 (4544)	−4024 (−18,633 to 10,586)	0.91 (0.08)	0.69 (0.13)	0.22 (−0.06 to 0.49)	−18,561	0.74	0.77	0.8	4385 (2910 to 5860)	5208 (3714 to 6701)	6236 (4708 to 7764)

TABLE 20 Randomised controlled trial: results of the cost-effectiveness analyses (day 1 to 36 weeks' corrected gestational age) (continued)

Scenario	Trial arm, mean (SE) cost (£)			Trial arm, mean (SE) cost (£)				Probability of cost-effectiveness at threshold			NMB (£) at threshold		
	CGM	Standard care	Incremental cost (£) (95% CI)	CGM	Standard care	Incremental effectiveness (95% CI)	ICER	£1000	£5000	£10,000	£1000 (95% CI)	£5000 (95% CI)	£10,000 (95% CI)
Wolverhampton N68	79,446 (6431)	88,220 (5321)	−8774 (−25,199 to 7651)	0.82 (0.12)	0.69 (0.15)	0.13 (−0.26 to 0.51)	−69,708	0.79	0.8	0.81	7539 (5856 to 9222)	7954 (6170 to 9737)	8473 (6553 to 10,392)
Southampton N73	56,614 (12,085)	61,969 (7603)	−5355 (−32,051 to 21,341)	1	0.83 (0.1)	0.17 (−0.04 to 0.37)	−32,129	0.81	0.81	0.82	5994 (2283 to 9705)	6904 (3220 to 10,589)	8043 (4386 to 11,700)
Amsterdam ND3	72,631 (16,207)	75,867 (8455)	−3236 (−38,650 to 32,177)	1 (0)	0.75 (0.17)	0.25 (−0.08 to 0.58)	−12,945	0.67	0.68	0.71	4415 (162 to 8669)	5810 (1521 to 10,099)	7553 (3212 to 11,893)
Stratification by gestational age at birth													
Extremely preterm (< 28 weeks' gestation)	84,532 (2548)	87,024 (2423)	−2492 (−8872 to 3888)	0.88 (0.06)	0.64 (0.06)	0.24 (0.08 to 0.4)	−10,443	0.81	0.88	0.91	2524 (1874 to 3174)	3493 (2824 to 4162)	4705 (4004 to 5406)
Very preterm (28–32 weeks' gestation)	59,983 (3187)	57,829 (2146)	2154 (−5541 to 9849)	0.93 (0.05)	0.79 (0.08)	0.14 (−0.05 to 0.33)	15,365	0.37	0.4	0.45	−1506 (−2304 to −707)	−911 (−1720 to −102)	−169 (−1001 to 664)
Stratification by sex													
Male	74,004 (3800)	81,783 (3860)	−7779 (−17,801 to 2243)	0.91 (0.05)	0.6 (0.08)	0.31 (0.12 to 0.5)	−25,123	0.93	0.96	0.99	7580 (6559 to 8602)	8816 (7763 to 9870)	10,361 (9262 to 11,460)
Female	72,839 (3641)	71,301 (2778)	1538 (−6991 to 10,067)	0.88 (0.06)	0.78 (0.07)	0.1 (−0.07 to 0.27)	15,381	0.33	0.35	0.37	−1732 (−2592 to −872)	−1333 (−2200 to −466)	−835 (−1717 to 48)
								£10,000	**£30,000**	**£50,000**	**£10,000 (95% CI)**	**£30,000 (95% CI)**	**£50,000 (95% CI)**
Secondary analysis													
Imputed costs and cases of BPD averted, covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.66 (0.17)	0.52 (0.12)	0.14 (−0.28 to 0.56)	−20,368	0.82	0.82	0.81	4466 (4167 to 4764)	7440 (6920 to 7959)	10,414 (9645 to 11,183)
Imputed costs and cases of NEC averted, covariate adjusted	73,505 (2758)	76,382 (2258)	−2877 (−10,026 to 4272)	0.87 (0.05)	0.71 (0.06)	0.16 (0 to 0.33)	−17,568	0.88	0.94	0.97	4726 (3923 to 5529)	7937 (6986 to 8888)	11,149 (9971 to 12,327)

a Subgroup analysis by site could not be performed for Oxford (N36), Surrey (N74), Barts (N85), Bristol (N86), Leeds (N87), Leicester (N88) or Barcelona (SP3) because of insufficient number of observations.
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FIGURE 16 Randomised controlled trial: (a) CEAC and (b) scatterplot at intervention period for 80% threshold of adequate glucose control, imputed and covariate adjusted.
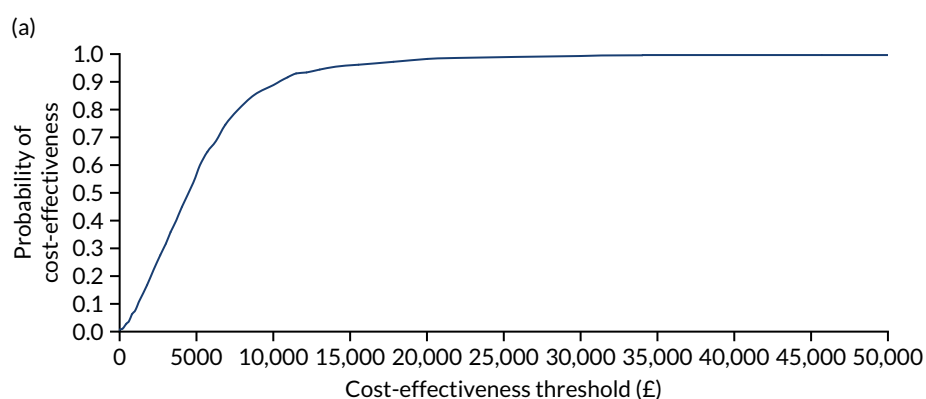
FIGURE 17 Randomised controlled trial (a) CEAC and (b) scatterplot at intervention period for 80% threshold of adequate glucose control, complete case and covariate adjusted. (*continued*)
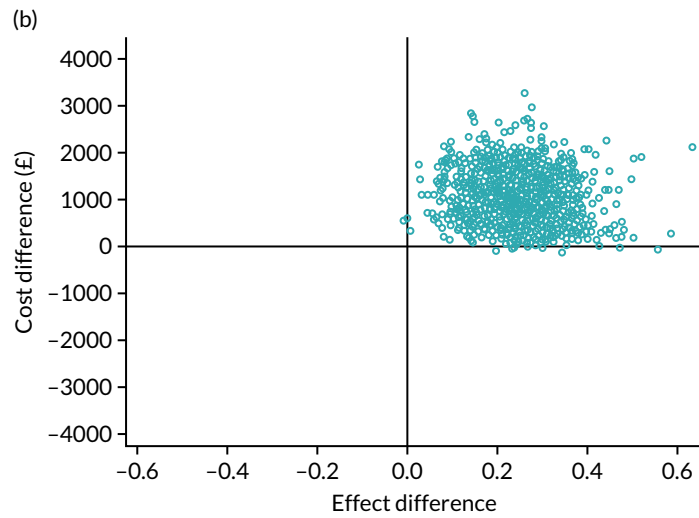
FIGURE 17 Randomised controlled trial (a) CEAC and (b) scatterplot at intervention period for 80% threshold of adequate glucose control, complete case and covariate adjusted.
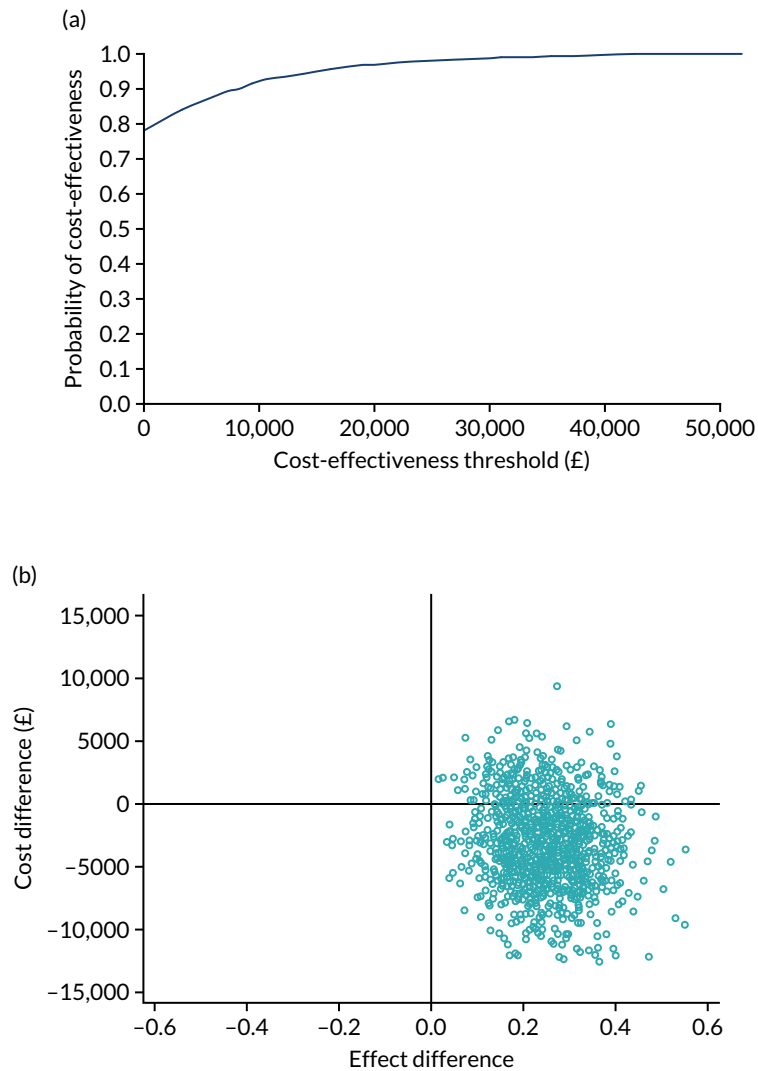
FIGURE 18 Randomised controlled trial: (a) CEAC and (b) scatterplot over entire follow-up period for 80% threshold of adequate glucose control, imputed and covariate adjusted.

(a)

(b)
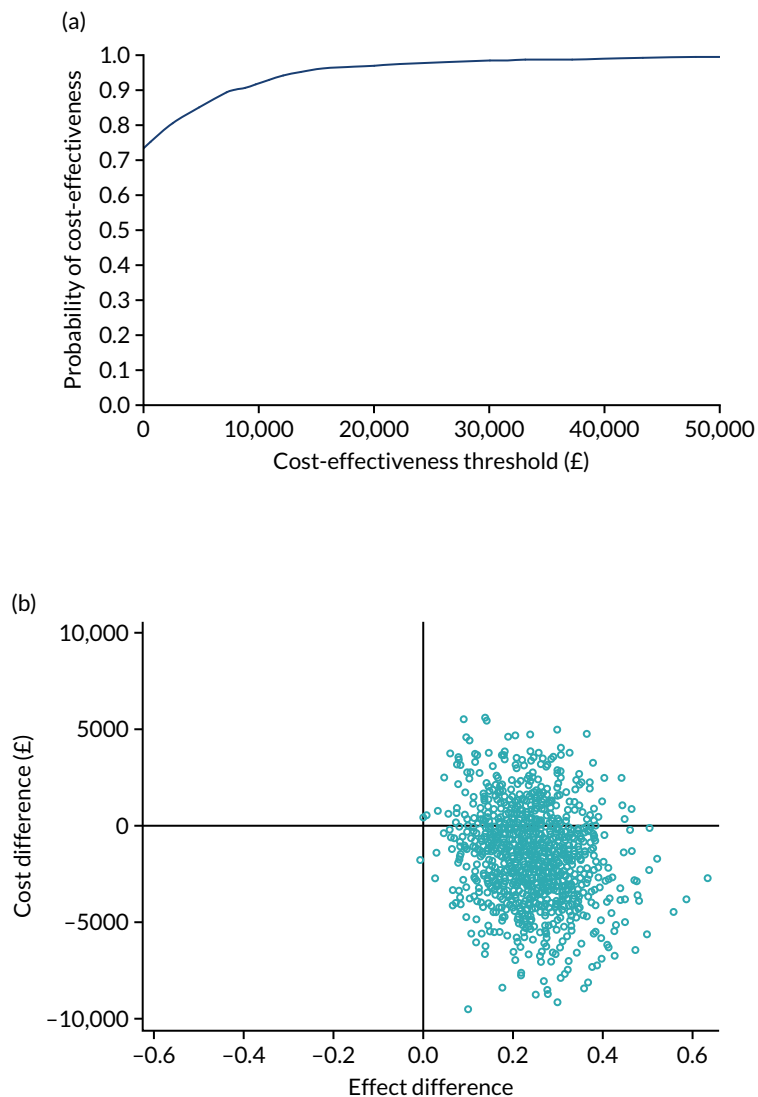
FIGURE 19 Randomised controlled trial: (a) CEAC and (b) scatterplot at entire follow-up period over 80% threshold of adequate glucose control, complete case and covariate adjusted.

remained similar, with £10,354 for the CGM group and £9749 for the standard-care group, but effectiveness varied. However, the pattern of increased effectiveness of CGM remained consistent across the scenarios when using different levels of adequate glucose thresholds. The results presented in *Table 20* support this finding. The notable difference is that CGM becomes the dominant strategy in health economic terms in the sensitivity analyses (see *Table 20*) because of the lower costs of CGM compared with standard care. In brief, the sensitivity analyses generally support the findings of the base-case analyses.

Subgroup analyses

Subgroup analyses were performed using the variables of site, gestational age and sex. A few study sites were dropped because the number of observations was insufficient. In all study sites presented in *Table 19*, effectiveness was greater in the CGM arm than in the standard-care arm and costs were also higher [except in site N42 (Norwich)] than in the standard-care group. Subgroup analyses based on gestational age at birth and sex demonstrated the same pattern, that is that costs and effectiveness were generally higher in the CGM arm than in the standard-care arm. Another notable finding was that costs were lower for male infants than female infants in the subgroup analyses.

Secondary outcome analyses

Secondary outcome analyses were performed using the two outcomes of NEC and BPD. For these outcomes, increased effectiveness can be interpreted as reduced cases of NEC and BPD and, hence, the denominator of the ICER has been inverted. The secondary outcome analyses revealed that, when the analysis is restricted to the 7-day intervention period, CGM averts more cases of BPD and NEC, but with higher costs, than standard care. Different cost-effectiveness threshold values were adopted for the secondary outcome analyses, namely £10,000, £30,000 and £50,000. The secondary outcomes displayed in *Table 20* show that the probability of cost-effectiveness of CGM reached 80% at a £10,000 cost-effectiveness threshold. In the secondary analyses reported in *Table 19*, mean costs were higher in the CGM arm (mean cost difference £605, 95% CI –£379 to £1589) than the standard-care arm. When valued over a time horizon extending to 36 weeks' corrected gestational age (see *Table 20*), the effectiveness followed the same pattern as the base-case analysis, but the costs were lower for CGM (mean cost difference –£2877, 95% CI –£10,026 to £4272) than standard care, making CGM dominant in health economic terms.

Chapter 6 REACT trial discussion

Discussion

This study demonstrates that CGM can be used to guide the use of insulin in preterm infants. The use of CGM leads to a reduction in exposure to hyperglycaemia and is also associated with a lower incidence of prolonged periods of hypoglycaemia. Previous studies found that the use of insulin in preterm infants led to an increased risk of hypoglycaemia, which was often clinically silent.[21,64] In contrast, this study showed that CGM allowed the safe titration of insulin, as well as highlighting clinically silent episodes of hypoglycaemia, in the standard-care group.

The strength of the study is that our findings on glucose exposure are not biased by the frequency of blood glucose sampling, as continuous data were available in both study arms. The accuracy of CGM at low glucose thresholds and the potential impact of glucose levels used for calibration remain controversial. However, CGM provides more detailed data on both glucose variability and the duration of exposure to any given target level, and it is increasingly apparent that these two parameters are more important than any prespecified threshold. Further analyses will be undertaken to explore the relationship between sensor and blood glucose levels in the trial.

The study highlights the wide variation in patterns of glucose control between infants and the significant difficultly for clinical staff in managing these infants with infrequent intermittent blood glucose monitoring. Furthermore, it demonstrates the challenges for staff in designing simple clinical guidelines for management of glucose control when the responses to interventions can be so varied. Comparison of mean daily sensor glucose and insulin infusion rates suggests that CGM led to earlier use of insulin, which prevented the early rise in glucose levels. Those in the standard-care arm received similar total levels of insulin during the intervention period but insulin was infused in the second half of the week and was associated with higher glucose levels. The significant interaction effects between treatment and both sex and first sensor glucose value are in keeping with expectations from clinical practice. This suggests that the most significant benefits are achieved in male infants and those with higher early glucose levels. The underlying pathophysiology driving this warrants further investigation.

The effect size is small, but similar to the clinically important difference of 10% that was prespecified in the sample size calculation. The effect size may have been limited by a number of factors, including compliance with the guideline for standard care, number of CGM data and improvements in standard care over time. In this context, in the CGM group, the sensor glucose level was recorded on the CRF > 90% of the time; however, the percentage of time during which the rate of insulin infusion was recorded when the glucose was > 8 mmol/l was only 54%. This may be because the guideline was designed to support clinical management, not to be a strict protocol. It may reflect the clinical team choosing to change rates of dextrose infusion rather than starting insulin. Alternatively, in some units that recruited only a few infants, proactive use of the CGM data and guideline was limited by the nature of intensive care (i.e. where the study outcomes are dependent on a large number of clinical staff being confident to deliver the study intervention over a 24-hour period). Increased use in these units may have led to further increases in time in target range, with increasing confidence in the accuracy of the sensor glucose level and the potential benefits of a more proactive approach allowing even better targeting of glucose control.

However, an increase from this level is remarkable, given the higher than predicted percentage of time within the target range of 84% (from 58% in initial masked data and 78% in the feasibility trial). This increase in time in the target range in the standard-care arm may be the result of changes in clinical practice either unrelated or related to the study. An increased emphasis placed on the importance of

glucose control while undertaking the trial may well have had an impact on the care of infants in the standard-care arm, a common phenomenon in the setting of a RCT.

Although not powered for clinical outcomes, a number of exploratory outcomes were explored. There were more deaths in the standard-care arm than in the CGM arm (6% vs. 2%), but the difference did not reach statistical significance. It was anticipated that the use of CGM might lead to increased insulin treatment and nutritional intake, and therefore have an impact on growth. However, there were no differences between study arms in total insulin infusion rates or nutritional intakes over the first week of life, and there were no differences in growth parameters. More infants in the standard-care arm (12%) than in the CGM arm (5%) required surgery for PDA, but the difference did not reach statistical significance and might be related to differences in fluid management. In the case of the exploratory outcome of incidence of NEC, CGM was associated with significantly reduced risk (OR 0.33, 95% CI 0.13 to 0.78; $p = 0.01$), with 28% of infants in the standard-care arm being diagnosed with NEC, compared with 13% of infants in the CGM arm. There is evidence to link hyperglycaemia with increased risk of microbial gut translocation.[65] However, larger studies would be needed to confirm such a link.

Compared with the feasibility study, more difficulties with initial insertion and sensor calibration were experienced in this trial.[1] This was initially thought to be because of the lack of experience of the procedure in the sites. Although site training was undertaken, and staff were provided with an online training video and a 24-hour helpline, it was challenging to support staff remotely. This was particularly the case given that this new procedure needed to be undertaken within a short, time-critical window after birth. The MiniMed 640G System and Enlite sensor are not specifically designed for neonatal use and this presents challenges to their use in this setting. The inserter provided cannot be used because of the small amount of subcutaneous tissue in preterm infants as the normal insertion angle of 90° would result in the needle passing through the subcutaneous tissue into muscle and other tissues below. The rate of successful insertion varied between centres. It was difficult for some individuals to gain significant experience and confidence within a study setting when undertaking a procedure infrequently. In discussion with Medtronic plc, it was suggested that the introducer itself plays a role in optimising the condition of the sensor after insertion by ensuring a rapid and smooth insertion technique.

Furthermore, because of the display of error codes on the MiniMed 640G System, it was difficult to always be clear as to the primary reason for 'sensor failure' and whether this was failure of insertion or a calibration error. There were substantially more calibration errors with the MiniMed 640G System than with the Paradigm Veo System (used in the feasibility study). This was discussed and reviewed in collaboration with Medtronic plc. A number of changes to the MiniMed 640G System algorithm were made to improve safety and increase accuracy at low threshold. These included (1) the use of artefact detection, such that signal dips that were deemed to not reflect true physiological glucose levels were filtered by the algorithm; (2) changes to signal threshold limits, which is the allowable range of interstitial signal that the algorithm can use; and (3) reduction in the calibration ratio limit (i.e. the difference between blood glucose and the sensor glucose). These factors, combined with the introduction of a lockout following two consecutive error codes during calibration, led to increased reports of failure to calibrate and loss of sensor data.

Lessons learned included the fact that the increased calibration error rate seen in some infants (particularly in the first 24 hours after birth) may have been because of high glucose variability and not failed sensor insertion. In some infants, the sensor was demonstrated to benefit from additional 'wetting time' to be able to generate sufficient signal for a reading. In both situations, allowing additional time for the sensor to settle in, either a few hours or, in the study setting, overnight, led to successful calibration and further monitoring. This is similar to the situation in lipodystrophy patients, in whom more time may be required prior to the first calibration to allow for 'wetting' of the sensor. In addition, staff were advised to avoid calibration when glucose levels were changing rapidly or immediately after one calibration error. This was counterintuitive in an intensive care setting, but prevented sensor lockout.

There were more deaths in the standard-care arm than in the CGM arm (six vs. two), but the difference did not reach statistical significance. Importantly, there were no SAEs related to the use of the devices in

this extremely vulnerable population or related to episodes of infection at the sensor site. Despite the challenges for staff of undertaking the paperwork required for such a trial, both staff and parents reported that they felt that CGM improved clinical care. The inclusion of a number of centres in both the UK and Europe make these results generalisable to a range of neonatal units that care for extremely preterm infants.

Limitations of the study include potential bias to study recruitment resulting from a short recruitment window of 24 hours, meaning that many infants' parents were not approached. This may have biased the study towards infants born in the local recruiting centre. We were unable to blind staff to the study intervention, but compliance with blinding of the CGM data in the standard-care arm was good. The lack of data for a number of infants could also lead to bias, but there was no significant difference in the outcomes based on full analysis and per-protocol populations, suggesting that the findings are robust. The study was limited by its dependence on a large number of clinical staff being confident to deliver the study intervention throughout a 24-hour period. Rapid developments in sensor and Bluetooth® technology (Bluetooth Special Interest Group, Kirkland, WA, USA), newer generations of sensors that do not require calibration and centralised platforms for closed-loop insulin delivery may further support the use of CGM in these infants.

Interpretation of the results of the economic evaluation was constrained by an absence of external evidence, either from external guidelines, or from stated or revealed preference studies, on economic values associated with health changes resulting from adequate glucose control or for health changes associated with the secondary clinical outcomes. Consequently, our assessments of cost-effectiveness rely on hypothetical cost-effectiveness threshold values for improvements in the relevant clinical outcomes. Furthermore, the economic evaluation was limited to the time horizon of the trial, extending to 36 weeks' corrected gestational age. The effects of CGM for targeting glucose control in neonates on longer-term economic costs and health consequences, including its potential to prevent the sequelae of NEC and BPD, remain a topic for future research.

In conclusion, this study demonstrates that CGM can safely guide the use of insulin and lead to a reduction in exposure to hyperglycaemia in extremely preterm infants. In addition, CGM is associated with a high probability of cost-effectiveness. Despite challenges, both staff and parents reported that they felt that CGM improved the clinical care of these infants. Further studies will be important to evaluate the longer-term impact of targeting glucose control on clinical outcomes.

The trial results in context

This study is in keeping with previous studies that have used CGM in the newborn population to monitor glucose levels and has highlighted clinically silent episodes of both hyperglycaemia and hypoglycaemia.[37,66] However, previous studies of CGM in infants have been much smaller, single centre and included a very small number of extremely preterm infants. These infants are those known to be most at risk of glucose dysregulation, in whom glucose control is most challenging and who have the highest risk of mortality and morbidity. It is these infants in whom any intervention has the potential to have the most clinical impact (on both morbidity and mortality). In this context, the higher rate of NEC in the standard-care group than in the CGM group, alongside evidence to link hyperglycaemia with increased risk of microbial gut translocation, warrants further investigation,[65] with larger studies needed to confirm such a link.

This study demonstrates that CGM can safely guide the use of insulin and lead to a reduction in exposure to hyperglycaemia without increasing the risk of hypoglycaemia in extremely preterm infants. The international multicentre design of this study suggests that the intervention can be safely applied across a range of practices considered as standard neonatal care and outside centres specialising in using CGM. Despite challenges, both staff and parents reported that they felt that the use of CGMs improved the clinical care of these infants. Further studies will be important to evaluate the longer-term impact of targeting glucose control on clinical outcomes.

Chapter 7 Closed-loop study

Introduction

The wide variation in individual insulin sensitivity and limited staff resources within intensive care make it challenging for the full potential of CGMs to be realised.[1] Adaptive computerised algorithms utilising blood glucose measurements have been evaluated in adults[67–69] and neonates undergoing intensive care.[37,70] The addition of frequent glucose levels obtained by CGM allows the development of closed-loop systems, as recently investigated in adult intensive care patients.[71,72] This study hypothesised that closed-loop insulin delivery, based on subcutaneous CGM, could be more effective in targeting glucose control in extremely preterm infants than CGM with insulin therapy and a guideline.

Aim

To pilot the use of a closed-loop system for glucose control using CGM.

Methods

Study design

This was a single-centre feasibility study in infants recruited from the NICU at the Cambridge University Hospitals NHS Foundation Trust. All parents of eligible infants admitted to the unit within 48 hours of birth were approached (if a member of the research team was available to do so). The study applied a randomised open-label parallel design, with infants randomised to CGM alone supported by a guideline or to CGM with an additional intervention period of closed-loop CGM. Research Ethics Committee approval and informed written parental consent were obtained prior to study procedures. Eligibility criteria included birthweight $\leq$ 1200 g and aged $\leq$ 48 hours. Infants were excluded if they had a major congenital malformation or an underlying metabolic disorder, or if the mother's pregnancy had been complicated by diabetes. Criteria were chosen based on previous data that identified these infants as at most risk of glucose dysregulation, while avoiding potential bias.[21]

A real-time CGM device was inserted in all infants and remained in situ for up to 7 days. The guideline advised on the use of insulin or additional dextrose support. For a prespecified period of 24 hours, between 48 and 72 hours post birth, a closed-loop system controlled glucose in infants during the closed-loop intervention, whereas infants in the control group continued to receive CGM alongside the guideline. This window for closed-loop intervention was preselected to be a standard time from birth in all infants to allow time for informed parental consent to be obtained and because previous data (from masked CGMs) had shown this to be the time when hyperglycaemia is most prevalent.[21] Randomisation applied the minimisation methods using the Minim randomisation software (version 1, London School of Hygiene and Tropical Medicine, London, UK), with stratification according to gestational age and birthweight.

Common study procedures

With the exception of glucose control over the prespecified period, all other aspects of care were identical between treatment groups. Blood glucose monitoring was undertaken on the POC glucose StatStrip meter. Actrapid® insulin (Novo Nordisk, Bagsværd, Denmark) at a concentration of 25 units/kg in 50 ml of 0.9% saline was used in both treatment groups. For CGM, an Enlite sensor was inserted by hand into the lateral thigh of each infant and linked to the Paradigm Veo for display of the sensor glucose concentration. Outside the intervention period (48–72 hours), CGM data were used in combination with the guideline by

the clinical team to guide glucose control in all infants. Nurses calibrated the CGM device at least once every 12 hours, with a blood glucose measurement taken on the POC glucose StatStrip meter.

Paper guideline

The guideline for insulin delivery has previously been described.[1] It provided guidance based on the absolute sensor glucose value, as well as glucose trends. If sensor glucose levels are outside the target range, the guideline recommends review of clinical care and the dextrose infusion rate, and that modification of insulin delivery be considered, which could be instigated by the nurse at cotside. The insulin and dextrose were delivered by Alaris™ pumps (CareFusion, San Diego, CA, USA).

Closed-loop glucose control between 48 and 72 hours

The closed-loop system comprised (1) an Enlite sensor, (2) a laptop computer running a model predictive control algorithm and (3) two Alaris syringe pumps. We used a control algorithm based on the model predictive control approach,[71,72] optimised and tuned in silico using a computer simulation environment validated for glucose control in the critically ill,[73] aiming to keep sensor glucose levels between 4 and 8 mmol/l. The algorithm calculated insulin requirements or, at low glucose values, 20% dextrose infusion rates based on real-time sensor glucose values. A study nurse entered sensor glucose values into the laptop and modified insulin and dextrose pumps, as directed by the control algorithm, every 15 minutes. During the closed-loop intervention, Actrapid insulin in a concentration of 25 units/kg in 50 ml of 0.9% saline was used to allow for finer-dose titration in accordance with the algorithm. The algorithm calculations utilised a compartment model of glucose kinetics,[74] describing the effect of insulin on sensor glucose excursions. The algorithm was initialised using an infant's weight and adapted itself to a particular infant by updating two model parameters: (1) a rapidly changing glucose flux, correcting for errors in model-based predictions; and (2) a slowly changing estimate of an insulin rate to maintain normoglycaemia. The individualised model forecasted plasma glucose excursions over a 1.5-hour prediction horizon when calculating the insulin rate and a 30- to 40-minute horizon when calculating the dextrose rate. Information about enteral or parenteral nutrition was not provided to the algorithm. A reference blood glucose value was used every 6 hours for calibration of the glucose sensor. If sensor readings were not available because of sensor failure or loss of data capture, then hourly blood glucose levels were used to inform the algorithm for up to 4 hours. At this time, the algorithm continued to provide advice every 15 minutes.

Assessments and data collection

Demographic and clinical characteristics were collected with the following antenatal variables based on clinical diagnoses recorded in the maternal medical file: antenatal steroids (having received at least one dose prior to delivery), prolonged rupture of membranes (a rupture > 24 hours prior to delivery), hypertension and chorioamnionitis. All blood glucose measurements, insulin administration, type and volume of enteral and parenteral nutrition, and additional intravenous glucose administration were recorded from the time of randomisation to the end of CGM.

Statistical analysis

The outcome measures and the statistical analysis plan were agreed in advance. The primary outcome was a comparison of the time that sensor glucose was in the glucose target range of 4–8 mmol/l between the study arms. Secondary outcomes were time spent with sensor glucose levels between 2.6 and 10 mmol/l, prevalence of hyperglycaemia (percentage of time sensor glucose is > 10 mmol/l) and mean (and SD) sensor glucose level. Safety end points included frequency of hypoglycaemia (any blood glucose levels < 2.6 mmol/l) and other AEs. Sample size was selected to reflect this study's status as a pilot to ensure that we had comparable control data, while minimising patient exposure. Formal power calculations were not performed and all analyses were based on intention to treat. An independent *t*-test was used to compare normally distributed variables. Non-normally distributed variables were compared using a Mann–Whitney *U*-test. Calculations were carried out using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA). Values are given as mean (SD) or median (IQR). *p*-values < 0.05 were considered statistically significant.

Results

Twenty-one infants were randomly assigned to the study arms, but one infant in the control group died within 48 hours of birth and so was excluded from the analyses. The baseline characteristics of the two groups (n = 20) were similar (*Table 21*). There were no significant problems with sensor insertion or removal, with only one infant (in the control group) having to have a sensor replaced, as there was no connection to the monitor. All 20 infants remained in the study throughout the intervention period from 48 to 72 hours, with similar numbers of sensor glucose data available for analysis in each group [for both study groups: median 24 (IQR 23.8–24) hours]. Control algorithm-directed insulin therapy was followed, at all times, during the prespecified 48- to 72-hour period. The maximum period of sensor signal loss during the closed loop was 3.5 hours, during which hourly blood glucose values were used by the control algorithm. There was minimal loss of data for the remainder of the study. One infant in the control arm was transferred out of the unit on study day 5 and one infant in the closed-loop arm died on study day 6, and so no further data could be collected for either infant. Therefore, the mean duration of collection of glucose data was 137 (SD 16.4) hours in the control arm and 136 (SD 8.7) hours in the closed-loop arm.

Glucose control and insulin and dextrose administration between 48 and 72 hours
There was no difference between the study groups in the baseline (48 hours) mean sensor glucose level (*Table 22*). During the intervention period, the median time spent in the target range of sensor glucose level (i.e. 4–8 mmol/l) was significantly higher in the closed-loop arm (91%, IQR 78–99%) than in the control arm (26%, IQR 6–64%) ($p < 0.001$). This was equivalent to 22 (IQR 19–24) hours in the closed-loop group, compared with 6 (IQR 1–15) hours in the control group. Similarly, the time spent in the wider target range of 2.6–10 mmol/l was higher in the closed-loop group (median 100% vs. median 84%). This was because the median percentage of time with sensor glucose values > 10 mmol/l was lower in the control arm than in the closed-loop arm (16% compared with 0%). There was no difference in the time spent with sensor glucose levels < 2.6 mmol/l. The median sensor glucose level was lower in the closed-loop arm (6.2 mmol/l, IQR 6.1–7.1 mmol/l) than in the control arm (8.6 mmol/l, IQR 7.4–11.1 mmol/l) ($p = 0.002$). Glucose variability, as measured by the SD of sensor glucose, was similar ($p = 0.6$).

TABLE 21 Closed-loop study: baseline demographic data[3]

Demographic data	Closed-loop arm (N = 10)	Control arm (N = 10)
Gestational age at birth (weeks), mean (SD)	27.0 (2.4)	27.5 (2.8)
Birthweight (g), mean (SD)	962 (164)	823 (282)
Sex (male-to-female)	5 : 5	5 : 5
Antenatal variable, n (%)		
Antenatal steroids	10 (100)	9 (90)
Maternal smoking	1 (10)	2 (20)
Chorioamnionitis	2 (20)	3 (30)
PROM[a]	4 (40)	4 (40)
Hypertension	1 (10)	1 (10)

PROM, prelabour rupture of membranes.
a   Defined as rupture of membranes for > 24 hours.
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TABLE 22 Closed-loop study: comparison of glucose control, insulin delivery and nutritional intake during the intervention period (48–72 hours post birth)[3]

Variable	Closed loop arm (n = 10)	Control arm (n = 10)	p-value
Time spent with sensor glucose level (%)			
4–8 mmol/l[a]	91 (78–99)	26 (6–64)	< 0.001
2.6–10 mmol/l	100 (94–100)	84 (46–98)	0.1
> 10 mmol/l	0 (0–6)	16 (2–54)	0.1
< 2.6 mmol/l	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.7
Baseline sensor glucose level (mmol/l)	7.9 (6.9–11.5)	8.2 (7.0–12.4)	0.2
Mean sensor glucose level (mmol/l)	6.2 (6.1–7.1)	8.6 (7.4–11.1)	0.002
SD of sensor glucose level (mmol/l)	1.0 (0.8–1.9)	1.3 (0.9–2.5)	0.6
Episodes of blood glucose < 2.6 mmol/l[b]	1	0	1
Nutritional intake			
Insulin (units/kg/hour)	0.04 (0.03–0.07)	0.02 (0.00–0.11)	0.4
Dextrose (mg/kg/minute)	8.4 (7.2–10.3)	8.5 (4.2–10.6)	0.6
Protein (g/kg/day)	3.2 (2.5–4.1)	3.5 (1.6–4.1)	1
Lipid (g/kg/day)	1.8 (1.0–1.8)	1.4 (0.9–2.2)	0.9
Trophic feeds	4	4	1

a Primary end point.
b Present at start of closed-loop study period prior to computer algorithm advice being initiated.

Notes
Data are presented as median (IQR).
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Summative glucose profiles and insulin delivery are provided in *Figure 20*. Nine out of the 10 infants in the closed-loop group had received insulin prior to the 24-hour intervention, with the one remaining infant being started on insulin during the 24-hour closed-loop period. For comparison, four infants in the control arm received insulin prior to the intervention period and eight infants received insulin during the intervention period. Four infants in the closed-loop arm received additional 20% dextrose for short periods during the intervention period (up to 3.5 hours). The mean infusion rate in these infants ranged from 0.13 to 0.53 ml/kg/hour, with the highest rate being infused in an infant who was hypoglycaemic prior to the start of the closed-loop intervention. There was no statistical difference in the total amount of insulin infused or nutritional intake between the study groups during the 24-hour intervention period.

Glucose control and insulin and dextrose administration between 72 and 160 hours
In the post-intervention period, after 72 hours, there was a trend of increased time in both glucose target ranges (i.e. 4–8 mmol/l and 2.6–10 mmol/l) in the closed-loop arm compared with the control arm (*Table 23*), but these differences did not reach statistical significance.

Nutrition and clinical care
All infants received parenteral and enteral nutrition in accordance with the standard local neonatal unit protocol. During the closed-loop intervention period, between 48 and 72 hours, four infants in each study group were receiving minimal amounts of trophic feeds. In the post-intervention period, after 72 hours, there was no difference between the two study groups in the volume of milk received (see *Table 23*).
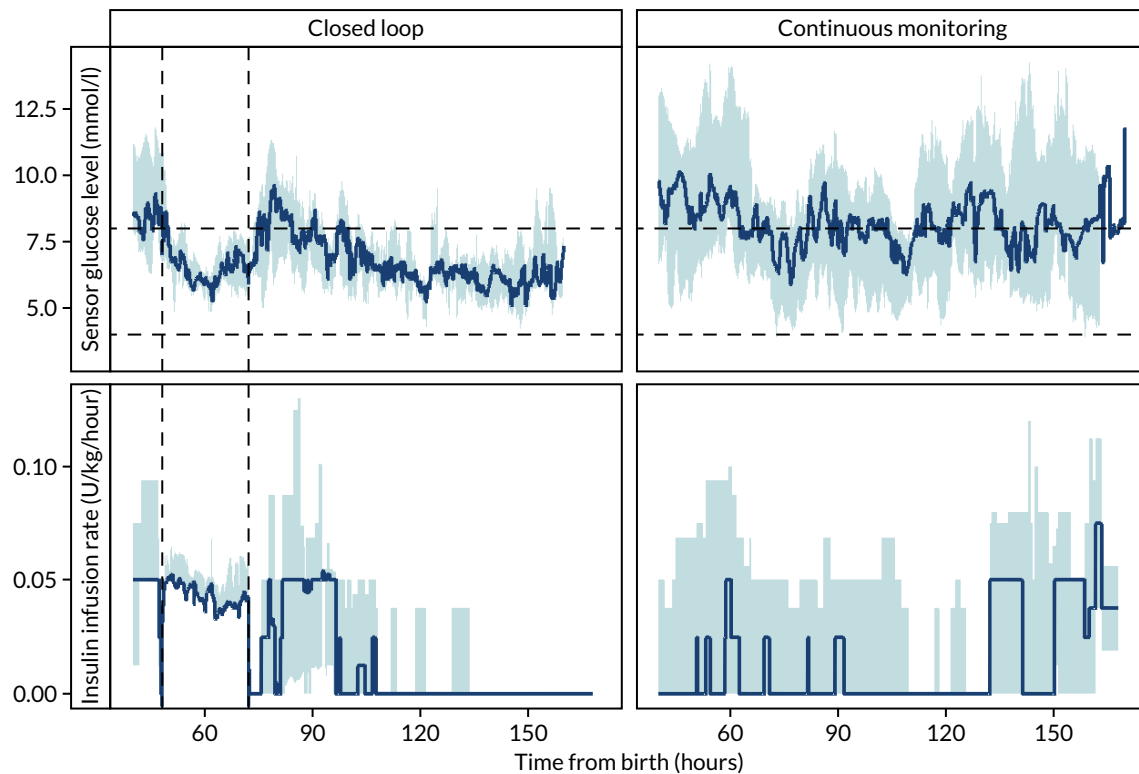
FIGURE 20 Closed-loop study: glucose control and insulin delivery.[3] Median (IQR) sensor glucose level and insulin infusion rate in infants randomised to closed-loop management or CGM with paper guideline (control). The closed-loop intervention period is denoted by the vertical lines and the glucose target range of 4–8 mmol/l is denoted by horizontal lines. The shaded area represents the IQR of sensor glucose values and insulin infusion rates, respectively. Reproduced with permission from Beardsall *et al.*[3] This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

None of the infants received hydrocortisone, but seven infants in the control arm and two infants in the closed-loop arm received inotropes during the first week. During the intervention period, the median number of blood glucose values taken per day was 5.5 (IQR 4.8–6.6) in the control arm and 6.3 (IQR 5.1–6.5) in the closed-loop arm. Over the whole study period, the median number of blood glucose values taken per day was 5.1 (IQR 4.3–5.4) in the control arm and 5.3 (IQR 4.6–5.8) in the closed-loop arm.

Safety

No reported concerns about the sensor site, in terms of inflammation or infection, were reported either during the study or after removal of the sensor. Two infants in the closed-loop arm experienced documented episodes of hypoglycaemia, with a blood glucose level < 2.6 mmol/l. One episode occurred when checking the baseline blood glucose prior to the start of the closed-loop intervention. At that time, maintenance fluids were being changed, but no insulin was being infused. The second episode was on day 6 and, again, this was associated with a change of maintenance fluids. A further two infants experienced periods (after the 72-hour closed loop) when sensor glucose levels fell below 2.6 mmol/l, but the blood glucose level at that time was documented to be above 2.6 mmol/l. In the control arm, no infants had a documented blood glucose value of < 2.6 mmol/l. One infant in the control arm experienced an episode lasting 205 minutes when the sensor glucose fell to < 2.6 mmol/l (blood glucose level was not checked at this time). None of the infants was on insulin and there was no clinical evidence of hypoglycaemia in these infants during any of these episodes.

TABLE 23 Closed-loop study: comparison of glucose control, insulin delivery and nutritional intake during the post-intervention period (72–160 hours post birth)[3]

Variable	Closed loop arm (*n* = 10)	Control arm (*n* = 10)	*p*-value
Time spent with sensor glucose level (%)			
4–8 mmol/l	64 (39–90)	42 (30–55)	0.05
2.6–10 mmol/l	95 (79–97)	78 (61–97)	0.2
> 10 mmol/l	3 (1–21)	22 (3–36)	0.2
< 2.6 mmol/l	0.0 (0.0–0.8)	0.0 (0.0–0.2)	0.7
Mean sensor glucose level (mmol/l)	7.0 (6.8–8.5)	8.3 (7.3–9.2)	0.2
SD of sensor glucose level (mmol/l)	1.7 (1.5–2.1)	1.7 (1.3–2.8)	0.8
Episodes of blood glucose < 2.6 mmol/l	1	0	1
Nutritional intake			
Insulin (units/kg/hour)	0.02 (0.00–0.04)	0.03 (0.00–0.05)	0.4
Dextrose (mg/kg/minute)	9.4 (7.0–10.6)	8.7 (5.4–10.9)	0.5
Protein (g/kg/day)	3.7 (2.7–4.3)	3.8 (2.9–4.4)	1
Lipid (g/kg/day)	2.0 (1.5–2.9)	1.8 (1.2–2.8)	0.6
Oral milk intake (ml/kg/day)	4.4 (3.5–11.5)	5.0 (0.5–13.0)	0.7

Notes
Data are presented as median (IQR).
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Discussion

To the best of our knowledge, this study is the first to show that a closed-loop system utilising subcutaneous glucose measurements to guide insulin delivery may improve glucose control in extremely preterm infants. This new approach could represent a step change in care, providing greater safety and tighter control, while minimising staff time at bedside and changes in fluid/insulin treatment. Compared with CGM alone, the closed-loop intervention increased threefold the percentage of time when sensor glucose was in the target range of between 4 and 8 mmol/l. In the high-intensity and high-cost setting of NICUs, these preliminary data support further development of closed-loop systems with real-time glucose-responsive insulin and dextrose delivery to support the care of these infants.

Reflecting the current controversy regarding optimal targets for glucose control in NICUs, we adopted a moderate glucose target range of between 4 and 8 mmol/l, rather than the tight glycaemic regimen of KU Leuven and Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) studies.[16,75,76] These moderate target ranges represent physiological in utero levels,[77] and the upper threshold reflects a postnatal glucose level that has been associated with increased mortality and morbidity in preterm infants.[10] However, the optimal target range for glucose levels in these infants is still to be determined and this study does not resolve this long-standing debate in the field. Instead, it shows how an automated system can be used to achieve control to a given target range.

Different strategies are currently utilised to target glucose control in the preterm infant, each with different risks and benefits. A reduction in dextrose load risks compromised nutritional intake, whereas insulin therapy can lead to hypoglycaemia. The level of insulin use in this study is likely to reflect both

the extreme prematurity of the infants recruited and the current practice in the NICU, which aims to 'optimise' nutritional delivery. In this study, there were no episodes of hypoglycaemia related to advice from the closed-loop algorithm, but CGM highlighted clinically silent episodes of hypoglycaemia in both study arms, independent of insulin use. The prevalence of hypoglycaemia was comparable to that reported by others in this population (27%)[64] and to that reported using masked CGM, which highlights prolonged periods of clinically silent hypoglycaemia.[21]

The CGM devices were calibrated using the StatStrip meter, which is validated for use in neonates and has US Food and Drug Administration approval for use in intensive care.[78] These meters are the standard of care for clinical management in the neonatal unit. Although there remains controversy regarding the clinical significance of clinically silent episodes of hypoglycaemia detected by CGM, there is recent evidence of an association between these episodes and substantially increased risk of impaired executive function and visual motor difficulty at 4.5 years.[79,80]

The frequency of blood glucose sampling in preterm infants is typically much lower than in adults and children in intensive care, and therefore CGM has the potential to have an even greater impact. Differences in frequency of blood glucose monitoring may have had an impact on the level of glucose control. However, among infants in the control arm, more than four blood glucose samples were taken every 24 hours in the first 3 days of life. Notably, the insulin administered in the intervention arm was more diluted than that used in the control group to allow for more frequent changes in dose titration. Despite randomisation, more infants in the control arm received inotropes during the first week, and inotropic drugs will reduce insulin secretion and insulin sensitivity. However, given the pattern of improved glucose control during the intervention period, we do not think that these differences can account for the differences in glucose control that were observed.

Previous studies have explored the potential for CGM to guide changes in dextrose delivery,[37] although intervention still depended on staff responding to trends in sensor glucose or to alarms.[37] In contrast, in the present study, targeting of glucose control was proactively driven by the closed-loop algorithm, which responded to frequently sampled sensor glucose data. This study is unique in exploring a control approach belonging to the family of model predictive control algorithms and optimised on a validated computer simulation environment[73] prior to study commencement to ensure a favourable outcome.

The strengths of our study are the randomised controlled study design, and the comparability of the study groups and nutritional intakes. The study limitations include a small sample size, which means that, despite randomisation, baseline differences could remain between the study groups. Although the study groups appeared comparable, more infants in the control group than in the closed-loop group were on inotropes, and more infants in the intervention arm were on insulin at the start of study intervention. With such a design, it was not possible to blind the clinicians to the intervention. The study duration was short and, therefore, as it is known that insulin sensitivity varies over time from birth, it is important to explore how the algorithm works over longer periods.

In addition, this was a single-centre study and, as nutritional policies and practices vary between centres, it will be important to test the algorithm in different units with different nutritional strategies to test its generalisability. The algorithm was not designed to alter nutritional delivery, as this was predetermined by the clinical team, with the intervention designed as a simple adjunct to support targeting glucose control, alongside the clinical plan for nutritional support. Alternative designs might consider a combined approach to guide nutritional intake alongside insulin treatment. Further studies are required to explore the impact of a fully automated system with infusion pumps providing insulin and 20% dextrose under fully automated computer control.

To the best of our knowledge, this is the first randomised study to evaluate the feasibility of a closed-loop control based on CGM in preterm infants to guide insulin delivery to support glucose control. This closed-loop system appears to be a potential adjunct for targeting glucose control in preterm infants requiring intensive care and warrants further study.

Chapter 8 Conclusions

Implications for future health

These studies have demonstrated that CGM can support the targeting of glucose control in the extremely preterm infant without increasing the risk of hypoglycaemia. Staff felt that CGM improved the care of infants. The economic evaluation demonstrated that, over the first 7 days, CGM is, on average, more costly and more effective than standard care. Assuming cost-effectiveness thresholds of £1000, £5000 and £10,000 per additional case of adequate glucose control, respectively, the probability of cost-effectiveness of CGM reached 90% at approximately £6000, while the NMB associated with CGM became positive at a cost-effectiveness threshold of £5000. Over a time horizon extending to 36 weeks' corrected gestational age, CGM was less costly and more effective, on average, than standard care and was therefore dominant in health economic terms.

The international nature of the study means that the results are generalisable across a range of NICU settings. The findings highlight the need for specific developments in the technology to improve the utility of CGM devices for use in this unique population. They further demonstrate the potential of a 'closed-loop' system to support targeting of glucose control, which could help to reduce staff workload and therefore cost.

The feasibility study highlighted the potential of CGM to identify infants at risk of incipient hypoglycaemia, which may be silent in this population. This study was unusual in undertaking a robust assessment of a new medical device in NICU patients before its introduction into clinical practice. The importance of designing devices to address the unique physiological and pathological challenges presented by these infants needs to be emphasised. More robust pathways are needed to encourage the development and validation of devices for use in such vulnerable populations. It is also important to ensure that these devices can be introduced into clinical practice in a robust manner, which requires adequate support and training for staff so that the devices are used effectively and safely in this population. Further developments in technology involving 'closed-loop systems' would be important in NICUs to limit blood sampling and provide a more personalised approach to care.

Specific post-study reflections

Continuous glucose monitoring versus point-of-care blood glucose

Considerable controversy remains as to the best way to manage neonatal glucose control, primarily because of a lack of good evidence on which to base clinical practice.[81,82] Measurement of glucose levels has evolved greatly over the last 40 years, with CGM being introduced in the last 20 years. The increasingly rapid innovations in technology could open up the opportunity for better understanding and management of the many infants who present with disordered glucose levels.

Current clinical care depends on a spectrum of medical devices and a range of clinical practices regarding the frequency of glucose sampling. Standard care includes capillary, venous or arterial blood sampling, and POC devices that have the advantage of rapid results and small samples compared with the 'gold standard' of laboratory analyses, which can result in a significant delay before results are available.[83] CGM could provide consistency in terms of interstitial levels measured continuously in real time. Over the course of our studies, the regulatory landscape for CGM models has changed during the time of these studies from an adjunct to care (requiring confirmatory blood glucose levels) to one where some CGM models are approved as being accurate enough to be a standalone guide to insulin dosing in patients with diabetes.[84]

The fact that CGM measures not blood but interstitial glucose levels has given rise to some concern about its 'validity'. Even when CGM devices are calibrated to blood glucose levels, there can be differences, particularly in certain circumstances.[85] However, it can be argued that interstitial glucose levels provide much more useful physiological and, therefore, clinical information, as cellular glucose levels may be particularly relevant to neuroglycopenia and the developing brain.[85]

The acknowledged lag of up to 15 minutes in sensor glucose level compared with blood glucose levels needs to be placed in a clinical context. Although there may be a short lag of 15 minutes using CGM, the system still provides a continuous trend in real time. In contrast, the current standard of care using intermittent blood sampling can result in a delay of many hours between levels being checked. CGM can therefore reveal significant periods of clinically silent hypoglycaemia.[86,87] This was highlighted in our studies, in which falling sensor values highlighted the need for blood glucose levels to be taken.[1] However, there were no SAEs related to a 'falsely' reassuring sensor glucose level during an episode of hypoglycaemia. The detection of clinically silent hypoglycaemic episodes may be the most useful impact of CGM, highlighted by the association of such episodes with deficits in attention and visual acuity at 4.5 years.[79] Although, theoretically, this could lead to overmedicalisation, the potential to prevent harm should not be missed.

The unbiased nature of the CGM data also has the potential to help us better understand the physiology and pathology of changes in glucose levels. However, CGM devices are not currently licensed for use in the neonate and are not designed for ease of use with these infants. The next steps are to engage with the industry to address issues specific to this population.

The use of paper and computerised algorithms

This programme of studies involved the use of CGM technology combined with a variety of algorithms, both paper and computer based. The interventions should therefore be considered 'combined interventions'.

We purposefully designed the paper algorithm as a guideline and not as a protocol. Although a 'protocolised' approach to ensure compliance may be considered optimal within a clinical trial, it was clear that the complexity needed for such a paper protocol would have increased risk. This was based on our previous experience, which highlighted wide variation in drug infusions, clinical complications and interventions across multiple sites. During the feasibility study, the algorithm evolved, as early iterations that aimed to avoid hypoglycaemia resulted in infusions being stopped and restarted more often than was deemed optimal. The advice was simplified for use by nursing staff, without requiring formal changes in prescriptions (similar to following a sliding scale). This was important as it provided a safe framework for the nursing staff to be able to titrate insulin infusion rates based on sensor glucose trends over short periods of time and nursing staff took ownership of decision-making, with a more comprehensive approach to care.

The 'closed-loop' study was entirely exploratory, but dramatically demonstrated the potential impact of combing the wealth of data from CGM with a computer-based algorithm. It provided a more personalised approach to care. A fully automated system has the potential to optimise clinical care by targeting glucose control and reducing workload. However, there are significant challenges to realisation, including CGM technology designed for the preterm infant, manufacturing engagement with open access to sensor and pump data, and regulatory hurdles. However, this route clearly could have significant impact for infants and staff.

Device trials and future regulations

Large multicentre device trials are uncommon compared with drug trials, and very limited clinical data are required for devices to obtain CE marking. This is particularly relevant for the neonatal population, in whom the unique risks and benefits may not have been fully assessed.

This trial highlighted some of the challenges of undertaking device trials, highlighting both practical clinical complexities and the importance of working closely with the company, with complete transparency about developments in the technology during the study.

Prior to starting the feasibility study, the sensor technology had been redesigned from the Medtronic plc Sof-Sensor® to the Medtronic plc Enlite, with a change in the angle of insertion. This was an advance for the adult market, but made sensor insertion more challenging in our preterm infants, who have limited subcutaneous tissue. It was necessary to modify procedures and study guidance. Further modifications were made to the Enlite sensor (from Enlite to Enlite plus) during the studies to improve the accuracy of the sensor technology.

On completion of the feasibility study, a new monitor was due to be released to supersede the Paradigm Veo. The advantages included better accuracy at low glucose levels and a clearer user interface. Therefore, after consideration and discussion with the TSC about risk and benefits, a decision was made to use the latest model. However, it became apparent that changes to the algorithm were having an impact on the calibration frequency and lockout of sensors which then needed to be replaced. Discussions with the company revealed that changes made to the algorithm to provide better accuracy and safety led to increased error readings within our population. There were further modifications to the algorithm to address some of these issues during the study. These potentially subtle changes from a manufacturing perspective had a significant impact on our sensor failure rate at the beginning of the study, but could not have been anticipated. This shows that the rapid advances in the technology present clinical challenges and it is imperative that manufacturers and clinicians work together with complete transparency.

Clinical aspects

Training the large number of staff within a busy intensive care unit to use devices as part of a clinical trial requires significant resources, both financial and time. In our studies, the short recruitment window increased this challenge for recruiting sites, and therefore the provision of on-site training and an online training video, as well as a 24-hour helpline, was important. It was clear that the level of support required for an interventional device trial was greater than that for an investigational medicinal product study.

Recommendation for further research

The findings of the REACT project raise the following important questions that need to be addressed in follow-on studies:

- What is the impact of 'optimising' glucose control on long-term health outcomes?
- What is the optimal glucose target range for preterm infants?
- What is the impact of silent hypoglycaemia in these preterm infants?
- Can we design a CGM that is better suited to the unique physiology and pathology of the newborn?
- What is the physiological basis for the differences found between sexes?

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Patient and public involvement

In each of the studies, families on the neonatal unit were asked individually and during informal family meetings to review and advise on the language of the patient information sheets and consent forms. There were two parents on the TSC throughout the multicentre trial who provided helpful insight into optimising consent, including increasing engagement with midwifery colleagues. These parents also provided advice on the content of parental newsletters prior to distribution. We have drafted a newsletter in collaboration with the lay member of the TSC and will circulate this once we have confirmation of publication, initially to a small group of families and then to all families who participated in the trial.

Contributions of authors

Kathryn Beardsall (https://orcid.org/0000-0003-3582-183X) (Consultant in Neonatal Intensive Care/Clinical Lecturer) conceived the idea and original design of the study and was the chief investigator. She was involved in designing the final design and conduct of research, and was a member of the Trial Management Group (TMG) and the TSC. She was also involved in the development of the trial protocol, the conduct of research interpretation and the reporting of results, and she revised the manuscript for important intellectual content.

Lynn Thomson (https://orcid.org/0000-0002-6629-0237) (Research Nurse) was the lead nurse for the trial and was involved from the conception of the trial design, and was involved in the set up, conduct and acquisition of these research data.

Catherine Guy (https://orcid.org/0000-0002-9686-7623) (Study Manager) was the trial manger and was involved in the set-up, running and management of the trial.

Simon Bond (https://orcid.org/0000-0003-2528-1040) (Senior Trial Statistician) was a member of the TMG and TSC. He provided leadership of the statistical aspects of the trial.

Annabel Allison (https://orcid.org/0000-0002-9122-6341) (Trial Statistician) was a member of the trial management group. She undertook complex data analysis and produced relevant statistical reports.

Beatrice Pantaleo (https://orcid.org/0000-0003-4860-3743) (Data Manager) was a member of the TMG. She led on the design of the CRFs and MACRO database, and developed Pepepuz software to assist with validating and analysing the CGM data. She was also responsible for management of the trial data.

Stavros Petrou (https://orcid.org/0000-0003-3121-6050) (Investigator) was involved in the trial design and led on the health economic data analysis.

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Publications

Li T, Thomson L, Ogilvy Stuart A, Beardsall K. Glucose monitoring and management in the NICU – how are we doing? *Infant* 2017;**13**:182–6.

Saha P, Beardsall K. Perioperative continuous glucose monitoring in a preterm infant. *BMJ Case Rep* 2018;**2018**:bcr2018224728.

Beardsall K, Thomson L, Guy C, van Weissenbruch MM, Iglesias I, Muthukumar P, *et al.* Protocol of a randomised controlled trial of real-time continuous glucose monitoring in neonatal intensive care 'REACT'. *BMJ Open* 2018;**8**:e020816.

Beardsall K. Real time continuous glucose monitoring in neonatal intensive care. *Early Hum Dev* 2019;**138**:104844.

Stewart ZA, Thomson L, Murphy HR, Beardsall K. A feasibility study of paired continuous glucose monitoring intrapartum and in the newborn in pregnancies complicated by type 1 diabetes. *Diabetes Technol Ther* 2019;**21**:20–7.

Thomson L, Elleri D, Bond S, Howlett J, Dunger DB, Beardsall K. Targeting glucose control in preterm infants: pilot studies of continuous glucose monitoring. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F353–9.

Beardsall K, Thomson L, Elleri D, Dunger DB, Hovorka R. Feasibility of automated insulin delivery guided by continuous glucose monitoring in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:279–84.

Beardsall K, Thomson L, Guy C, Iglesias-Platas I, van Weissenbruch MM, Bond S, *et al*. Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. *Lancet Child Adolesc Health* 2021;**5**:265–73.

Petrou S, Kim S, Bond S, Allison A, Beardsall K, the REACT collaborative. Cost-effectiveness of real time continuous glucose monitoring to target glucose control in preterm infants. *Semin Perinatol* 2021;**45**:151392.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Thomson L, Elleri D, Bond S, Howlett J, Dunger DB, Beardsall K. Targeting glucose control in preterm infants: pilot studies of continuous glucose monitoring. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F353–9. https://doi.org/10.1136/archdischild-2018-314814

2. Beardsall K, Thomson L, Guy C, van Weissenbruch MM, Iglesias I, Muthukumar P, *et al.* Protocol of a randomised controlled trial of real-time continuous glucose monitoring in neonatal intensive care 'REACT'. *BMJ Open* 2018;**8**:e020816. https://doi.org/10.1136/bmjopen-2017-020816

3. Beardsall K, Thomson L, Elleri D, Dunger DB, Hovorka R. Feasibility of automated insulin delivery guided by continuous glucose monitoring in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:279–84. https://doi.org/10.1136/archdischild-2019-316871

4. Beardsall K, Thomson L, Guy C, Iglesias-Platas I, van Weissenbruch MM, Bond S, *et al.* Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. *Lancet Child Adolesc Health* 2021;**5**:265–73. https://doi.org/10.1016/S2352-4642(20)30367-9

5. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 2000;**106**:659–71. https://doi.org/10.1542/peds.106.4.659

6. Petrou S. The economic consequences of preterm birth during the first 10 years of life. *BJOG* 2005;**112**:10–15. https://doi.org/10.1111/j.1471-0528.2005.00577.x

7. Economides DL, Proudler A, Nicolaides KH. Plasma insulin in appropriate and small for gestational age fetuses. *Am J Obstet Gynecol* 1989;**160**:1091–4. https://doi.org/10.1016/0002-9378(89)90167-1

8. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, Ong K, *et al.* Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study. *J Pediatr* 2010;**157**:715–19.e1–3. https://doi.org/10.1016/j.jpeds.2010.04.032

9. Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. *Cochrane Database Syst Rev* 2009;**1**:CD007453. https://doi.org/10.1002/14651858.CD007453.pub2

10. Hays SP, Smith EO, Sunehag AL. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. *Pediatrics* 2006;**118**:1811–18. https://doi.org/10.1542/peds.2006-0628

11. Finberg L. Dangers to infants caused by changes in osmolal concentration. *Pediatrics* 1967;**40**:1031–4.

12. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. *J Perinatol* 2003;**23**:186–94. https://doi.org/10.1038/sj.jp.7210879

13. Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V, Kennedy KA. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. *J Perinatol* 2006;**26**:730–6. https://doi.org/10.1038/sj.jp.7211593

14. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, *et al.* Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;**345**:1359–67. https://doi.org/10.1056/NEJMoa011300

15. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of the critically ill? *Diabetologia* 2006;**49**:1722–5. https://doi.org/10.1007/s00125-006-0306-4

16. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, *et al.* Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009;**373**:547–56. https://doi.org/10.1016/S0140-6736(09)60044-1

17. Alexandrou G, Skiöld B, Karlén J, Tessma MK, Norman M, Adén U, Vanpée M. Early hyperglycemia is a risk factor for death and white matter reduction in preterm infants. *Pediatrics* 2010;**125**:e584–91. https://doi.org/10.1542/peds.2009-0449

18. Peters KL, Rosychuk RJ, Hendson L, Coté JJ, McPherson C, Tyebkhan JM. Improvement of short- and long-term outcomes for very low birth weight infants: Edmonton NIDCAP trial. *Pediatrics* 2009;**124**:1009–20. https://doi.org/10.1542/peds.2008-3808

19. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: hyperglycemia and glucose variability are associated with increased mortality and morbidity. *Pediatr Crit Care Med* 2008;**9**:361–6. https://doi.org/10.1097/PCC.0b013e318172d401

20. Beardsall K, Ogilvy-Stuart AL, Ahluwalia J, Thompson M, Dunger DB. The continuous glucose monitoring sensor in neonatal intensive care. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F307–10. https://doi.org/10.1136/adc.2004.051979

21. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, *et al.* Early insulin therapy in very-low-birth-weight infants. *N Engl J Med* 2008;**359**:1873–84. https://doi.org/10.1056/NEJMoa0803725

22. Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. *J Pediatr* 2010;**157**:198–202.e1. https://doi.org/10.1016/j.jpeds.2010.02.003

23. Schierenbeck F, Franco-Cereceda A, Liska J. Accuracy of 2 different continuous glucose monitoring systems in patients undergoing cardiac surgery. *J Diabetes Sci Technol* 2017;**11**:108–16. https://doi.org/10.1177/1932296816651632

24. Holzinger U, Warszawska J, Kitzberger R, Wewalka M, Miehsler W, Herkner H, Madl C. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. *Diabetes Care* 2010;**33**:467–72. https://doi.org/10.2337/dc09-1352

25. Price GC, Stevenson K, Walsh TS. Evaluation of a continuous glucose monitor in an unselected general intensive care population. *Crit Care Resusc* 2008;**10**:209–16.

26. De Block C, Manuel-y-Keenoy B, Rogiers P, Jorens P, Van Gaal L. Glucose control and use of continuous glucose monitoring in the intensive care unit: a critical review. *Curr Diabetes Rev* 2008;**4**:234–44. https://doi.org/10.2174/157339908785294460

27. Preiser JC, Chase JG, Hovorka R, Joseph JI, Krinsley JS, De Block C, *et al.* Glucose control in the ICU: a continuing story. *J Diabetes Sci Technol* 2016;**10**:1372–81. https://doi.org/10.1177/1932296816648713

28. Keenan DB, Cartaya R, Mastrototaro JJ. Accuracy of a new real-time continuous glucose monitoring algorithm. *J Diabetes Sci Technol* 2010;**4**:111–18. https://doi.org/10.1177/193229681000400114

29. Beardsall K, Dunger D. Insulin therapy in preterm newborns. *Early Hum Dev* 2008;**84**:839–42. https://doi.org/10.1016/j.earlhumdev.2008.09.013

30. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, VanWeissenbruch M, Midgley P, *et al.* Validation of the continuous glucose monitoring sensor in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F136–40. https://doi.org/10.1136/archdischild-2012-301661

31. International Organization for Standardization. *ISO 13485:2003. Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes.* URL: www.iso.org/standard/36786.html (accessed 12 February 2021).

32. International Organization for Standardization. *ISO/IEC 27001:2013. Information Technology – Security Techniques – Information Security Management Systems – Requirements.* URL: www.iso.org/standard/54534.html (accessed 12 February 2021).

33. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**1**:307–10.

34. Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, *et al.* An alternative sensor-based method for glucose monitoring in children and young people with diabetes. *Arch Dis Child* 2017;**102**:543–9. https://doi.org/10.1136/archdischild-2016-311530

35. Raizman JE, Shea J, Daly CH, Karbasy K, Ariadne P, Chen Y, *et al.* Clinical impact of improved point-of-care glucose monitoring in neonatal intensive care using Nova StatStrip: evidence for improved accuracy, better sensitivity, and reduced test utilization. *Clin Biochem* 2016;**49**:879–84. https://doi.org/10.1016/j.clinbiochem.2016.05.002

36. Schmelzeisen-Redeker G, Schoemaker M, Kirchsteiger H, Freckmann G, Heinemann L, Del Re L. Time delay of CGM sensors: relevance, causes, and countermeasures. *J Diabetes Sci Technol* 2015;**9**:1006–15. https://doi.org/10.1177/1932296815590154

37. Galderisi A, Facchinetti A, Steil GM, Ortiz-Rubio P, Cavallin F, Tamborlane WV, *et al.* Continuous glucose monitoring in very preterm infants: a randomized controlled trial. *Pediatrics* 2017;**140**:e20171162. https://doi.org/10.1542/peds.2017-1162

38. British Association of Perinatal Medicine. *Categories of Care 2011.* URL: https://hubble-live-assets.s3.amazonaws.com/bapm/attachment/file/43/CatsofcarereportAug11.pdf (accessed July 2021).

39. Department of Health and Social Care. *Reference Costs 2013–14.* URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/380322/01_Final_2013-14_Reference_Costs_publication_v2.pdf (accessed July 2021).

40. World Medical Association. *WMA Declaration of Helsinki – Ethical Principles For Medical Research Involving Human Subjects.* URL: www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects (accessed July 2021).

41. European Commission. *Overview.* URL: https://ec.europa.eu/health/md_sector/overview_en#new_regulations (accessed July 2021).

42. European Medicines Agency. *International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).* URL: www.ema.europa.eu/en/partners-networks/international-activities/multilateral-coalitions-initiatives/international-council-harmonisation-technical-requirements-registration-pharmaceuticals-human-use (accessed July 2021).

43. Petrou S, Kim S, Bond S, Allison A, Beardsall K, the REACT collaborative. Cost-effectiveness of real time continuous glucose monitoring to target glucose control in preterm infants. *Semin Perinato* 2021;**45**:151392. https://doi.org/10.1016/j.semperi.2021.151392

44. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013.* London: NICE; 2013.

45. Curtis LA, Burns A. *Unit Costs of Health and Social Care 2017.* URL: www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/ (accessed 1 August 2019).

46. NHS Employers. *NHS Terms and Conditions (AfC) Pay Scales – Annual*. URL: www.nhsemployers.org/pay-pensions-and-reward/agenda-for-change/pay-scales/annual (accessed 1 December 2018).

47. OpenDataNI. *Health Trust Reference Costs 2016–17*. URL: https://data.gov.uk/dataset/489e83d2-7b05-41e1-b8f3-c06c1a8a9de4/health-trust-reference-costs-2016-17 (accessed 1 December 2018).

48. Joint Formulary Committee. *British National Formulary*. London: BMJ Group and Pharmaceutical Press; 2018.

49. NHS. *NHS Blood and Transplant Price List 2017*. URL: http://hospital.blood.co.uk/media/28230/component-price-list-2016-2017.pdf (accessed 15 August 2018).

50. GOV.UK. *Advisory Fuel Rates*. URL: www.gov.uk/government/publications/advisory-fuel-rates/how-advisory-fuel-rates-are-calculated (accessed 1 August 2019).

51. Gomes M, Ng ES, Grieve R, Nixon R, Carpenter J, Thompson SG. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Med Decis Making* 2012;**32**:350–61. https://doi.org/10.1177/0272989X11418372

52. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Chichester: John Wiley & Sons; 2004.

53. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;**45**:1–68. https://doi.org/10.18637/jss.v045.i03

54. Horton NJ, Lipsitz SR. Multiple imputation in practice: comparison of software packages for regression models with missing variables. *Am Stat* 2001;**55**:244–54. https://doi.org/10.1198/000313001317098266

55. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. https://doi.org/10.1002/sim.4067

56. Cox NJ. Speaking Stata: a set of utilities for managing missing values. *Stata J* 2015;**15**:1174–85. https://doi.org/10.1177/1536867X1501500413

57. Moler C. *Numerical Computing with Matlab*. Philadelphia, PA: Society for Industrial and Applied Mathematics; 2004. https://doi.org/10.1137/1.9780898717952

58. Glick H, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. 2nd edn. Oxford: Oxford University Press; 2014. https://doi.org/10.1093/med/9780199685028.001.0001

59. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall; 1993. https://doi.org/10.1007/978-1-4899-4541-9

60. Briggs AH, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.

61. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–15. https://doi.org/10.1002/hec.903

62. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th edn. Oxford: Oxford University Press; 2015.

63. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, *et al.* Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess* 2015;**19**(14). https://doi.org/10.3310/hta19140

64. Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. *Pediatrics* 2012;**129**:639–47. https://doi.org/10.1542/peds.2011-2470

65. Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, *et al*. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 2018;**359**:1376–83. https://doi.org/10.1126/science.aar3318

66. Nally LM, Bondy N, Doiev J, Buckingham BA, Wilson DM. A feasibility study to detect neonatal hypoglycemia in infants of diabetic mothers using real-time continuous glucose monitoring. *Diabetes Technol Ther* 2019;**21**:170–6. https://doi.org/10.1089/dia.2018.0337

67. Cordingley JJ, Vlasselaers D, Dormand NC, Wouters PJ, Squire SD, Chassin LD, *et al*. Intensive insulin therapy: enhanced model predictive control algorithm versus standard care. *Intensive Care Med* 2009;**35**:123–8. https://doi.org/10.1007/s00134-008-1236-z

68. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, *et al*. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009;**35**:1738–48. https://doi.org/10.1007/s00134-009-1585-2

69. Pachler C, Plank J, Weinhandl H, Chassin LJ, Wilinska ME, Kulnik R, *et al*. Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. *Intensive Care Med* 2008;**34**:1224–30. https://doi.org/10.1007/s00134-008-1033-8

70. Le Compte A, Chase JG, Lynn A, Hann C, Shaw G, Wong XW, Lin J. Blood glucose controller for neonatal intensive care: virtual trials development and first clinical trials. *J Diabetes Sci Technol* 2009;**3**:1066–81. https://doi.org/10.1177/193229680900300510

71. Leelarathna L, English SW, Thabit H, Caldwell K, Allen JM, Kumareswaran K, *et al*. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. *Crit Care* 2013;**17**:R159. https://doi.org/10.1186/cc12838

72. Leelarathna L, English SW, Thabit H, Caldwell K, Allen JM, Kumareswaran K, *et al*. Accuracy of subcutaneous continuous glucose monitoring in critically ill adults: improved sensor performance with enhanced calibrations. *Diabetes Technol Ther* 2014;**16**:97–101. https://doi.org/10.1089/dia.2013.0221

73. Wilinska ME, Blaha J, Chassin LJ, Cordingley JJ, Dormand NC, Ellmerer M, *et al*. Evaluating glycemic control algorithms by computer simulations. *Diabetes Technol Ther* 2011;**13**:713–22. https://doi.org/10.1089/dia.2011.0016

74. Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, *et al*. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am J Physiol Endocrinol Metab* 2002;**282**:E992–1007. https://doi.org/10.1152/ajpendo.00304.2001

75. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, *et al*. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;**360**:1283–97. https://doi.org/10.1056/NEJMoa0810625

76. Finfer S, Heritier S, NICE Study Management Committee and SUGAR Study Executive Committee. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan. *Crit Care Resusc* 2009;**11**:46–57.

77. Economides DL, Nicolaides KH, Campbell S. Metabolic and endocrine findings in appropriate and small for gestational age fetuses. *J Perinat Med* 1991;**19**:97–105. https://doi.org/10.1515/jpme.1991.19.1-2.97

78. U.S. Food & Drug Administration. *FDA Recommendations for All Hospital Patients Including ITU*. URL: www.fda.gov/food/resources-you-food/healthcare-professionals (accessed July 2021).

79. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG, *et al.* Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 Years. *JAMA Pediatr* 2017;**171**:972–83. https://doi.org/10.1001/jamapediatrics.2017.1579

80. McKinlay CJD, Chase JG, Dickson J, Harris DL, Alsweiler JM, Harding JE. Continuous glucose monitoring in neonates: a review. *Matern Health Neonatol Perinatol* 2017;**3**:18. https://doi.org/10.1186/s40748-017-0055-z

81. Ogilvy-Stuart AL, Harding JE, Beardsall K. Thresholds for hypoglycaemic screening-a cause for concern? *Arch Dis Child Educ Pract Ed* 2019;**104**:33–4. https://doi.org/10.1136/archdischild-2017-314135

82. Cornblath M, Ichord R. Hypoglycemia in the neonate. *Semin Perinatol* 2000;**24**:136–49. https://doi.org/10.1053/sp.2000.6364

83. Beardsall K. Measurement of glucose levels in the newborn. *Early Hum Dev* 2010;**86**:263–7. https://doi.org/10.1016/j.earlhumdev.2010.05.005

84. Dexcom. *Dexcom G6® CGM System Receives CE Mark*. URL: https://dexcom.gcs-web.com/news-releases/news-release-details/dexcom-g6r-cgm-system-receives-ce-mark (accessed 26 May 2021).

85. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol Ther* 2009;**11**:11–16. https://doi.org/10.1089/dia.2009.0002

86. Wackernagel D, Dube M, Blennow M, Tindberg Y. Continuous subcutaneous glucose monitoring is accurate in term and near-term infants at risk of hypoglycaemia. *Acta Paediatr* 2016;**105**:917–23. https://doi.org/10.1111/apa.13479

87. Uettwiller F, Chemin A, Bonnemaison E, Favrais G, Saliba E, Labarthe F. Real-time continuous glucose monitoring reduces the duration of hypoglycemia episodes: a randomized trial in very low birth weight neonates. *PLOS ONE* 2015;**10**:e0116255. https://doi.org/10.1371/journal.pone.0116255

Appendix 1 Summary of protocol amendments

Amendment number	Date of submission	Details
1	17 December 2015	Protocol amendment (v2, dated 17 December 2015): • Minor amendments to protocol Parent information sheet (v4, dated 17 December 2015): • Minor amendments New study logo
2	4 August 2016	Protocol amendment (v3, dated 4 August 2015): • Clarification of reportable safety events following discussion with the MHRA (protocol, section 12)
3	4 August 2016	Addition of one site: • John Radcliffe Hospital, Oxford
4	2 December 2016	Protocol amendment (v4, dated 7 November 2016): • To enable the research team to receive parental/guardian verbal consent
5	16 December 2016	Addition of two sites: • Evelina London Children's Hospital, St Thomas' Hospital, London • Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh
6	9 March 2017	Addition of one site: • New Cross Hospital, Wolverhampton • Minor amendments to parent and clinical staff questionnaires
7	25 May 2017	Change of principal investigator at John Radcliffe Hospital, Oxford
8	28 July 2017	Request to extend study until 30 November 2018
9	14 September 2017	Addition of six sites: • St Michael's Hospital, Bristol • St Peter's Hospital, Chertsey • Leeds General Infirmary, Leeds • Leicester Royal Infirmary, Leicester • The Royal London Hospital • Princess Anne Hospital, Southampton
10	29 June 2018	Minor amendments, including: • Poster • QR code to access study video • Certificates for infants joining the study • Keep-in-contact card
11	7 August 2018	GDPR information sheet
12	21 September 2018	Request to extend study until 31 July 2019
13	6 December 2018	Minor amendments, including: • Christmas card/seasonal news • Short questionnaire for families to complete to confirm preferred method of contact and thoughts about the design of a follow-up study

GDPR, General Data Protection Regulation; QR, quick response.

Appendix 2 Trial Steering Committee terms of reference

Study/Trial Full Title: Real Time Continuous Glucose Monitoring in Neonatal
                          Intensive Care

Protocol short title: REACT (RCT)

IRAS ID: 168042

ISRCTN Number: 12793535

ClinicalTrials.gov Identifier (if applicable):

Investigational Medical Device: Real Time Continuous Glucose Monitoring with
                        paper-based algorithm

Chief Investigator: Dr Kathryn Beardsall

Sponsor: Cambridge University Hospitals NHS Foundation Trust and University of
         Cambridge

Introduction

The role of the Trial Steering Committee (TSC) is to provide overall supervision for the Real Time Continuous Glucose Monitoring in Neonatal Intensive Care on behalf of the Trial Sponsor and the Trial Funder and to ensure that the trial is conducted according to the guidelines for Good Clinical Practice (GCP), Research Governance Framework for Health and Social Care and all relevant regulations and local policies.

The background to this trial, its objectives, assessments, interventions, etc, is described in the trial protocol.

The purpose of this document is to define the roles and responsibilities of the trial TSC and to guide its activities, its relationship with other trial committees, its membership, and the format, purpose and timings of its meetings. The charter also describes the procedures for ensuring confidentiality and proper communication to and from the TSC and an outline of the content of the reports to be provided to the TSC.

Terms of reference

To provide advice, through its Chair, to the Trial Management Group (TMG), the Sponsor and the Trial Funder on all aspects of the trial.

To monitor and supervise the progress of the trial towards its overall objectives, review accrual and results of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the trial and the research question.

To ensure that the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society.

To ensure that all relevant approvals are obtained before a project begins

To agree proposals for substantial protocol amendments and provide advice to the TMG regarding approvals of such amendments.

To consider the recommendations of Ethics committees, the trial/study DMEC and/or other trial/study committees.

The TSC should inform the TMG if:

There are concerns about the safety of participants

Accrual is too low to provide meaningful results

It is evident that if the study continues it would fail to provide a clear benefit

To terminate the study or further adapt it based on safety and efficacy considerations.

Membership and Primary responsibilities of the TSC

The REACT TSC is a multidisciplinary group composed of the following members who have responsibility for the design, conduct and evaluation of the clinical research project and termination of the trial if deemed necessary. The committee comprises of 71% independent members, 29% non-independent members and 3 attendees and will maintain an approximate 75%/25% split of independent/non-independent members.

Chair: Professor Kate Costeloe (Independent)

Statistician: Professor Tim Cole (Independent)

Clinician: Dr Peter Watkinson (Independent)

Clinician: Dr Andrew Ewer (Independent)

Lay Member: Emma Avery (Independent)

Chief Investigator: Dr Kathryn Beardsall (Non-Independent)

Co-Investigator: Professor David Dunger (Non-Independent)

Senior Clinical Trials Coordinator/CCTU Representative: Dr Paula Kareclas (Attendee)

Trial Statistician: Dr Simon Bond (Attendee)

Study Manager: Catherine Guy (Attendee)

Members of the TMG:

Chief Investigator: Dr Kathryn Beardsall

Co-Investigator: Professor David Dunger

Study Manager: Catherine Guy

Research Nurse: Lynn Thomson

Study Statisticians: Dr Simon Bond and James Howlett (till Feb 2017);

Dr Julia Forman (Feb-Apr 17); Dr Annabel Allison

Senior Data Manager: Beatrice Panataleo

Senior Clinical Trials Coordinator: Dr Paula Kareclas

The Chief Investigator will nominate TSC members to NIHR EME (Funder) Programme Director who will then formally appoint the Chair and independent members.

The responsibility for calling and organising TSC meetings lies with the Chief Investigator in association with the Chair. The Chair assisted by the Chief Investigator is responsible for facilitating the meetings and to summarise discussions.

The TSC membership is for the duration of the trial. If any members leave the TSC, the Chief Investigator in discussion with the Chair should provide replacements and notify EME programme manager of independent members who will need to be formally appointed by the EME programme Director.

Agreements

TSC members should formally register their agreement to be a member of the committee as well as their agreement with the contents of the charter, trial confidentiality and should declare any potential conflicts of interest.

Independent members should complete and return a signed agreement and competing interests form provided at the end of this charter.

Responsibilities

The TSC on behalf of the Sponsor and Funder will have overall responsibility for the design and conduct of the trial and for safeguarding the rights, safety and wellbeing of participants. The TSC has the authority to suspend or terminate the Trial. The DMEC can make recommendations for such action to the TSC but the decision lies with the TSC. Responsibilities of the TSC to include:

Reviewing selection/recruitment/retention of participants and their management

Finalising and reviewing study protocol and other study documentation.

Determine if amendments to the protocol or changes to study conduct are required and deciding on changes to these and to study conduct in general. Any changes to trial documentation or conduct must be notified to the TSC.

Reviewing adherence to the protocol by Investigators and participants

Assessing the impact and relevance of external evidence

Assessing integrity and completeness of data collected

Monitoring the overall conduct of the trial, ensuring that it follows the standards set out in the guidelines of GCP, assessing the safety and efficacy of the interventions, recruitment figures and completion of trial assessments.

Reviewing, commenting and making decisions on extension requests.

Reviewing the recommendations of the DMEC and/or other study committees and suggesting appropriate action to the TMG

Monitoring the progress of study/trial and deciding on appropriate action in order to maximise the chances of completing it within the agreed timelines.

Considering new information relevant to the study e.g. results from other studies that may have a bearing to the conduct of the study and deciding on appropriate action.

Endorsing the annual report to the funder

The TSC may terminate the trial or modify the trial design in the event of a clear outcome derived from accumulating data or on the basis of information available from other sources or on safety grounds.

The TSC should be available to provide independent advice as required not just when meetings are scheduled.

The TSC should maintain confidentiality of all information it receives.

Members should not discuss confidential issues from their involvement in the study until the primary results have been published.

Role of the TSC Chair

Arrange the first meeting of the TSC with the assistance of the CI to agree contents of charter and set up schedule of meetings prior to recruitment of participants

Establish clear reporting lines – to the Funder, Sponsor etc

Become familiar with the role of the DMEC

Provide an independent, experienced opinion if conflicts arise between the needs of the research team, the Funder, the Sponsor and/or any other agencies

Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems

Ensuring that changes to the protocol are debated and endorsed by other members of the TSC

For decisions to be made, at least 2 independent members of the TSC should be present (including the chair) and a non-independent member (CI or Co-Investigator). Only members of the committee (not attendees) can vote.

TSC meetings

The responsibility for calling and organising a TSC meeting lies with the CI in association with the TSC Chair.

The study manager will organise these on behalf of the CI

Meetings will be in person and by teleconference

All TSC members will be provided with study documents (e.g. protocol, proposed statistical analysis plan (SAP), PIS, CRF etc) and the TSC report prior to the meeting.

The first TSC meeting should ideally be held face-to-face to discuss, revise and finalise the terms of reference, agree the content of the TSC charter and sign any declaration, and agree the frequency of the meetings.

It is anticipated that TSC meetings will be held every 6-8 months depending on progress of recruitment

Meetings can also be held at any time at the request of the CI or TSC chair

The final TSC meeting will be arranged when target recruitment is completed, all data collected and cleaned, and the database is locked. This final meeting will be held to discuss final/completed data and interpretation, and publication timeless. If the study is terminated prematurely, no final study meeting is required.

Attendance

Every effort will be made to ensure that all TSC members can attend the meetings. The study manager or delegate should try and find a date that enables this. The CI must try to attend all meetings, especially if major actions are expected.

Two independent TSC members (including the Chair) and a non-independent member (CI or Co-Investigator) need to be present for a meeting to take place.

If the TSC is considering major actions the TSC Chair should communicate with absent members, including the CI, as soon after the meeting as possible to determine whether they all agree. If there is disagreement amongst absent members a further meeting should be arranged with the full TSC.

Reporting

The DMEC will report directly to the TSC and submit regular reports to the TSC Chair.

Prior to a TSC meeting a report will be prepared by the TMG with input from the study manager, data manager and statistician and circulated to TSC members at least a week before the meeting.

On consideration of the information presented at these meetings, the TSC should provide recommendations of appropriate action in writing to the TMG who will be responsible for implementing any actions. The TSC may also provide feedback to the IDMEC and where appropriate to the Sponsor/Funder.

Minutes of the meeting including key points and actions will be prepared by the study manager. These minutes will describe the proceedings and include the recommendations of the TSC. All members of the TSC must agree the minutes and these will be signed off by the TSC Chair on behalf of all members. Minutes will be circulated to all TSC members, the TMG, the Sponsor and, if appropriate, the Trial Funder. Approved Minutes will be filed in the Trial Master File.

Decisions and recommendations by the TSC should be unanimous if not a vote may be taken. The role of the Chair is to summarise discussions and encourage consensus. Therefore, it is best for the chair to give her opinion last. It is important that the implications (ethical, statistical, practical, and financial) for the trial be considered before any decision is made.

Contents of the TSC Reports

An outline of the contents of the TSC report is given below:

Study synopsis in addition to current available evidence

Statistical consideration and design

Major protocol amendments

Patient screening

Eligibility violations

Protocol violations by investigators

Study accrual by month/total

Completeness and quality of data collected/CRF return

Data quality/monitoring

CRF return, entry into database

Baseline characteristics

Demographics

Disease characteristics

Safety reporting

Any matters affecting the trial

Latest DMEC report and DMEC recommendations

Conflicts of interest

TSC members should not have any apparent financial, scientific or intellectual conflict of interest that could prevent them from objectively reviewing the study protocol, interim and final data and giving advice to the TMG. TSC members should disclose to the Chair any other conflicts they consider relevant. Any members who develop significant conflicts of interest during the course of the trial should resign from the TSC.

Publication

Manuscripts that arise from the trial will be shared with the TSC and members will be able to comment. The TSC members and their affiliations will be acknowledged in reports of the trial.

References:

1. CCTU/GD018

2. MRC Guidelines for GCP in clinical trials (1998)

3. MHRA GCP Guide (2012)

Annexe 1
Agreement and competing interests form for independent members of the Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (REACT RCT) Trial Steering Committee.

Please complete the following document and return to:

Study Manager
REACT RCT Trial
University Department of Paediatrics
University of Cambridge
Box 116, Level 8
Cambridge Biomedical Campus
Hills Road
Cambridge CB2 0QQ

☐ I have read and understood the TSC charter version 1.0 dated 11 December 2014

☐ I agree to join the TSC for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidential

The avoidance of any perception that members of the TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial. Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests:

Table 1: Potential competing interests for independent members

1. Stock ownership in any commercial companies involved. 2. Stock transaction in any commercial company involved (if previously holding stock) 3. Consulting arrangements with the Sponsor 4. Frequent speaking engagements on behalf of the intervention 5. Career tied up in a product or technique assessed by the trial 6. Hand-on participation in the trial 7. Involvement in the running of the trial 8. Emotional involvement in the trial 9. Intellectual conflict e.g. strong prior belief in the trial's experimental arm 10. Involvement in regulatory issues relevant to the trial procedures 11. Investment (financial or intellectual) in competing products 12. Involvement in the publication

☐ **NO,** I have no competing interests to declare

☐ **YES,** I have competing interests to declare (please detail below)

_____
_____
_____

Name: _____

Signed:_____   Date: _____
    algorithm

Chief Investigator: Dr Kathryn Beardsall

Sponsor: Cambridge University Hospitals NHS Foundation Trust and University of
        Cambridge

Appendix 3 Data Monitoring Committee Charter

Trial Title: Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (RCT)

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust & University of Cambridge

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Independent Data Monitoring Ethics Committee DMEC Charter

Version 1.0   Date 10 March 2015
(Developed from DAMOCLES DMEC Charter Template v1. February 2005)

Authorised by:

Name: Dr Kathryn Beardsall	Role: Chief Investigator
Signature:	Date: 10 March 2015

Prepared by:

Name: Catherine Guy	Role: Trial coordinator
Signature:	Date: 10 March 2015

Table of Contents

CONTENT	CHARTER DETAILS
1. INTRODUCTION	
Name of trial	Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (REACT RCT)
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
Objectives of trial, including interventions being investigated	Randomised Controlled Trial 200 babies will be randomised 1:1 ratio between 1. Real time continuous glucose monitoring (rCGM) with paper based algorithm (Intervention) and 2. Standard clinical management with continuous glucose monitoring data blinded to the clinical team (Control) Purpose To evaluate efficacy, safety and utility of real time continuous glucose monitoring (rCGM) in Neonatal Intensive Care (NICU) Primary Objective ▪ To evaluate the efficacy of rCGM in helping control levels of glucose in the preterm infant ▪ To evaluate clinical acceptability in the preterm infant ▪ To assess safety in terms of risk for hypoglycaemia in the preterm infant Secondary Objective ▪ To evaluate the cost-effectiveness and NHS importance of such an intervention
Outline of scope of charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority and decision-making of the independent DMEC for the REACT RCT, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other committees.

CONTENT	CHARTER DETAILS
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the committee	To protect and serve REACT Trial patients (especially re: safety) and to assist and advise Chief Investigator and Trial Management Group (TMG) so as to protect the validity and credibility of the REACT Trial.
	To safeguard the interests of REACT Trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the REACT Trial.
Terms of reference	The DMEC should receive and review the progress and accruing data of the REACT Trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).
	The DMEC should inform the Chair of the TSC if, in their view:
	The results are likely to convince a broad range of
	clinicians, including those supporting the trial and
	the general clinical community, that one trial
	arm, or a subset of trial population, is clearly
	indicated or contraindicated, and there was a
	reasonable expectation that this new evidence
	would materially influence patient management
Specific roles of DMEC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main endpoints including safety data.
	- assess data quality, including completeness - monitor recruitment figures and losses to follow-up - monitor evidence for treatment differences in the main efficacy endpoints - monitor evidence for treatment harm (eg Serious Adverse Device Effects (SADEs), Adverse Device Effects (ADEs), Serious Adverse Events - review the report of suspected unexpected serious adverse reaction (SUSAR) and Unexpected Serious Adverse Device Effects (USADEs) provided by the trial team whenever occurs - decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated - suggest additional data analyses - advise on protocol modifications suggested by the TMG - monitor continuing appropriateness of patient information - monitor compliance with previous DMEC recommendations

CONTENT	CHARTER DETAILS
	• consider the ethical implications of any recommendations made by the DMEC
	• assess the impact and relevance of external evidence
	• maintain confidentiality of all trial information that is not in the public domain
	• protect validity and scientific credibility of the trial
3. BACKGROUND	
Protocol Input	All potential DMEC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g. a research ethics committee and Medicines and Healthcare products Regulatory Agency (MHRA). Therefore, if a potential DMEC member has major reservations about the trial (eg the protocol or the logistics) they should report these to the CI or trial coordinating team and may decide not to accept the invitation to join. DMEC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Meeting prior to Trial starting	The DMEC will meet before the trial starts to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the CI(s) and coordinating team. The DMEC should meet within one year of recruitment commencing.
	A dummy report will be provided to the DMEC members prior to their first meeting after recruitment commences to enable them to become familiar with the format data will be presented.
Safety Issues	All hypoglycaemic episodes will be recorded and reported if BG ≤2.2mmols/l. In addition the CI will notify DMEC of all safety events (SUSARs, USADEs and SADEs) when they occur.
Regulatory issues	MHRA and UK ethics approval will need to be obtained prior to recruiting UK participants and regulatory and ethics approval will be obtained prior to recruiting from each country.
DMEC contracts	DMEC members will not formally sign a contract but should formally register their assent to join the group by confirming (1) that they agree to be on the DMEC and (2) that they agree with the contents of this Charter. Any competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Observers attending any part of the meeting should sign a confidentiality agreement on the first occasion they attend all or part of a meeting (Annexe 2).

CONTENT	CHARTER DETAILS
4. COMPOSITION	
DMEC Membership	Membership should consist of a small number of members, who include at least one clinician experienced in the clinical area and at least one statistician. Additional members experienced in clinical trials should reflect the other specialities involved in the trial.
	The members should not be involved with the trial in any other way or have some competing interest that could impact on the trial. Any competing interests, both real and potential, should be declared. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. A short competing interest form should be completed and returned by the DMEC members to the trial coordinating team (Annexe 1).
	The independent members of the DMEC for this trial are:
	• Professor David Field - Professor of Neonatal Medicine - University of Leicester
	• Professor Diana Elbourne - Professor of Health Care Evaluation - London School of Hygiene and Tropical Medicine
	• Dr Jane Hawdon - Consultant Neonatologist - Barts Health NHS Trust
The Chair and the Chair's role	Professor David Field has agreed to be the Chair and is an internationally respected and experienced neonatologist with a breadth and depth of experience of serving on Clinical Trial DMECs.
The responsibilities of the DMEC statistician	Professor Diana Elbourne is the DMEC statistician who will provide independent statistical expertise.
	Trial Statistician for this trial is:
	• Dr Simon Bond - Senior Trial Statistician
The responsibilities of the trial statistician	The trial statistician will have the overall responsibility for producing the report to the DMEC and will participate in DMEC meetings, guiding the DMEC through the report, participating in DMEC discussions and, on some occasions, taking notes.
The responsibilities of the trial coordinating team	The trial coordinator/or project manager of trial will help the trial statistician to produce the non-confidential sections of the DMEC report. The trial coordinator/or project manager may attend open sessions of the meeting.
The responsibilities of the CI and other members of the TMG	The CI may be asked, and should be available, to attend open sessions of the DMEC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Section 6. Organisation of DMEC Meetings).

CONTENT	CHARTER DETAILS
5. RELATIONSHIPS	
Relationships with CI(s), other trial committees (TSC, TMG), sponsor and regulatory bodies	The DMEC will report directly to the TSC and submit regular reports to the TSC Chair.
	The DMEC will have access to data by trial arm and be responsible for monitoring these data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The DMEC will be responsible for providing recommendations to the TSC regarding early termination of the trial for safety but decisions regarding early termination lie with the TSC.
Clarification of whether the DMEC are advisory (make recommendations) or executive (make decisions)	The TSC is oversight body of the trial and is delegated this role by the sponsor. The DMEC does not make decisions about the trial, but rather makes recommendations to the TSC.
Payments to DMEC members	Members will be reimbursed for travel and accommodation where required. No other payments or rewards are given.
	DMEC members should not use interim results to inform trading in pharmaceutical shares, shares in companies making and marketing devices and careful consideration should be given to trading in stock of companies with competing products.
6. ORGANISATION OF DMEC MEETINGS	
Expected frequency of DMEC meetings	DMEC will review safety on a patient number basis and plans to meet following recruitment of the first 50 patients and then again following recruitment of a total of 125 patients.
	However, the exact frequency of meetings will depend on trial events. The wishes of the DMEC and needs of the trial coordinating team will be considered when planning each meeting.
	An unplanned DMEC meeting may be called by the Chair or requested by the TMG if there is an emergency concern on the safety of participants.
Meeting Format	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.
Organization of Meeting	The format of the REACT DMEC meetings will be:

CONTENT	CHARTER DETAILS
	1. Open session: Introduction and any "open" parts of the report that need to be discussed between DMEC and CI or other members of the trial coordinating team and if necessary representatives of the sponsor, funder or regulator. 2. Closed session: Discussion of "closed" parts of the report by DMEC and Trial Statistician if requested or others specifically invited by DMEC
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Content of material to be available in open sessions	Open sessions: Accumulating information relating to recruitment and data quality including data return rates will be presented. Safety event details and compliance of using paper based algorithm will be presented.
Content of material to be available in closed sessions	Closed sessions: In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.
Blinding to treatment allocation	The DMEC will not be blinded to the treatment allocation.
The people who will see the accumulating data and interim analysis	The confidential accumulating data and interim analysis by treatment allocation will be seen by the DMEC members and the trial statistician(s). DMEC members do **not** have the right to share confidential information with anyone outside the DMEC, including the CI.
Responsibility for identifying and circulating external evidence (eg from other trials/ systematic reviews)	The CI, TMG and the trial coordinating team will collate any such information for the presentation in an open session. Other Trial DMECs may pass information to REACT DMEC for consideration.
To whom the DMEC will communicate the decisions/ recommendations that are reached	The DMEC will report its recommendations in writing to the TSC. This will be copied to the trial statistician (or trial coordinator) and if possible, should be sent via the trial statistician and trial coordinator in time for consideration at a TSC meeting. If the trial is to continue the report will be sent to the TSC from the DMEC to include a summary paragraph suitable for trial promotion purposes. (See Annexe 3.) In its communications, the DMEC should be careful not to relay any unnecessary information to the TSC: the TSC membership might have members of TMG. The DMEC should take care to protect the CI from interim trial results where possible.
Timing of Reports	The DMEC will receive the trial report at least 2 weeks before any meetings.

CONTENT	CHARTER DETAILS
What will happen to the confidential papers after the meeting	The DMEC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMEC members should destroy all interim reports. A copy of all the reports will be held at the Cambridge Clinical Trials Unit.
8. DECISION MAKING	
What decisions/recommendations will be open to the DMEC	Possible recommendations could include: • No action needed, trial continues as planned • Early stopping for clear evidence of harm due to a treatment in terms of its safety profile, strong evidence in favour of either treatment in terms of the primary endpoint, or external evidence. • Extending recruitment or extending follow-up • Sanctioning and/or proposing protocol changes
The role of formal statistical methods	There is no planned interim analysis but DMEC will meet following recruitment of 50 participants. Formal statistical methods will be used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.
How decisions or recommendations will be reached within the DMEC	The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last. Every effort should be made for the DMEC to reach a unanimous decision. If the DMEC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical and financial) for the trial be considered before any recommendation is made.
Members who cannot attend	If the report is circulated before the meeting, DMEC members who will not be able to attend the meeting may pass comments to the DMEC Chair for consideration during the discussions.
What happens to members who do not attend meetings	If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMEC.
Whether different weight will be given to different endpoints (eg safety/efficacy)	The role of the DMEC will be to review safety.

CONTENT	CHARTER DETAILS
9. REPORTING	
To whom will the DMEC report their recommendations/ decisions, and in what form	The DMEC will write to the TSC and trial coordinator within 3 weeks. A copy of the DMEC recommendation will be stored in the trial master file.
The Chair will be responsible for organizing minutes to be taken and stored.	Minutes will be taken for open and closed sessions. The DMEC Chair should sign off any minutes or notes. Minutes from open sessions to be circulated to TMG.
What will be done if there is disagreement between the DMEC and the body to which it reports	If the DMEC has serious problems or concerns with the TSC decision a joint meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired in the first instance by the TSC Chair. If there remains a disagreement the sponsor will nominate an independent expert to chair the meeting.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there may be a meeting to allow the DMEC to discuss the final data with the key members of TMG and give advice about data interpretation
The information about the DMEC that will be included in published trial reports	DMEC members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMEC meetings should be included in the body of this paper.
Whether the DMEC will have the opportunity to approve publications, especially with respect to reporting of any DMEC recommendation regarding termination of a trial	The DMEC will be given the opportunity to read and comment on publications before submission. This will usually be concurrent with the trial investigators and independent members of the TSC reading and commenting. The commenting period will usually be 2 to 3 weeks.
Any constraints on DMEC members divulging information about their deliberations after the trial has been published	The DMEC may discuss issues from their involvement in the trial when permission is agreed with the overseeing TSC.

Figures

Relationship between TMG, DMEC and TSC

Annexe 1: Agreement and potential competing interests form

Real Time Continuous Glucose Monitoring in the Neonatal Intensive Care

Please complete the following document and return to the REACT RCT Co-ordinator.

(Please initial box to agree)

☐	I have read and understood the DMEC Charter version 1.0, dated 10 March 2015
☐	I agree to join the DMEC for this trial
☐	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a DMEC may be biased in some fashion is important for the credibility of the decisions made by the DMEC and for the integrity of the trial.

Possible competing interest should be disclosed via the Cambridge Clinical Trials Unit – Paediatric Theme (CCTU-PT). In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMEC member should remove the conflict or stop participating in the DMEC. Table 1 lists potential competing interests.

☐	No, I have no competing interests to declare
☐	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

Name: _____

Signed: _____   Date: _____

Table 1: Potential competing interests

Stock ownership in any commercial companies involved
Stock transaction in any commercial company involved (if previously holding stock)
Consulting arrangements with the Sponsor (including Chief Investigator for other Cambridge Clinical Trials Unit – Cancer Theme trials)
Frequent speaking engagements on behalf of the intervention
Career tied up in a product or technique assessed by trial
Hands-on participation in the trial
Involvement in the running of the trial
Emotional involvement in the trial
Intellectual conflict e.g. strong prior belief in the trial's experimental arm
Involvement in regulatory issues relevant to the trial procedures
Investment (financial or intellectual) or career tied up in competing products
Involvement in the publication in the form of authorship

Annexe 2: Agreement and confidentiality agreement for observers

Real Time Continuous Glucose Monitoring in Neonatal Intensive Care

Please complete the following document and return to the Trial Co-ordinator.

(Please initial box to agree)

☐	I have received a copy of the DMEC Charter version 1.0, dated 10 March 2015
☐	I agree to attend the DMEC meeting on ___/____/_____
☐	I agree to treat as confidential any sensitive trial information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____   Date: _____

Annexe 3: Suggested report from DMEC to TSC where no recommendations are being made

[Insert date]

To: Professor Kate Costeloe

Via: Trial statistician

Dear Professor Costeloe

The Data Monitoring Ethics Committee (DMEC) for the REACT (RCT) met on [meeting date] to review its progress and interim accumulating data. [List members] attended the meeting and reviewed the report.

The DMEC should like to congratulate the investigators and trial team on the running of the trial and its recruitment, data quality and follow-up. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [specify protocol version number and date] with no changes.

We shall next review the progress and data [provide approximate timing]

Yours sincerely,

Professor David Field

On behalf of the DMEC

DMEC members:

Professor David Field

Professor Diana Elbourne

Dr Jane Hawdon

Annexe 4: REACT RCT Contacts

REACT (RCT) TMG contacts

Chief Investigator:

Dr Kathryn Beardsall

Trial Co-ordinator:

Catherine Guy

Trial Statistician

Dr Simon Bond

REACT (RCT) TSC Independent Chair Contacts

Professor Kate Costeloe

Appendix 4 Randomised controlled trial: additional analyses

TABLE 24 Randomised controlled trial: model-fitting results – sensitivity analyses of the primary outcome

Model	Covariate	Estimate (SE)	95% CI	*p*-value
Linear regression weighted by number of sensor glucose observations	Intercept	80 (3.4)	73.3 to 86.7	< 0.001
	CGM vs. standard	8.5 (2.6)	3.4 to 13.6	0.001
	N36 (reference N01)	−5 (15)	−34 to 25	0.8
	N42	7.0 (5.5)	−3.9 to 17.9	0.2
	N43	−0.04 (3.8)	−7.6 to 7.5	0.99
	N68	1.7 (4.0)	−6.1 to 9.5	0.7
	N73	3.6 (5.4)	−7.1 to 14.2	0.5
	N74	10 (12)	−15 to 35	0.4
	N85	8.3 (6.4)	−4.4 to 21	0.2
	N86	−21 (8.7)	−38.1 to −3.9	0.02
	N87	−17 (12)	−40 to 7	0.2
	N88	−26.5 (7.2)	−40.8 to −12.2	< 0.001
	ND3	6.3 (6.2)	−6 to 18.6	0.3
	SP3	9.2 (7.6)	−5.9 to 24.3	0.2
	Gestation ≥ 26 weeks	6.1 (3.3)	−0.4 to 12.6	0.07
RSD = 15.8				
Linear regression adjusted for start time of first sensor glucose and first sensor glucose	Intercept	82.8 (4.7)	73.6 to 92	< 0.001
	CGM vs. standard	9.1 (2.6)	3.9 to 14.3	< 0.001
	Time from birth (hours) to first sensor glucose measurement	0.04 (0.13)	−0.23 to 0.3	0.8
	First sensor glucose measurement (mmol/l)	−2.3 (0.55)	−3.4 to −1.21	< 0.001
	N36 (reference N01)	−12.8 (12.3)	−37.1 to 11.6	0.3
	N42	2.8 (6)	−9.1 to 14.6	0.6
	N43	0.005 (4)	−8 to 8	0.999
	N68	−2.8 (4.2)	−11 to 5.5	0.5
	N73	−0.4 (5.3)	−10.9 to 10	0.9
	N74	3.8 (12.2)	−20.2 to 27.9	0.8
	N85	4.9 (6.6)	−8.1 to 18	0.5
	N86	−14.6 (8.5)	−31.4 to 2.3	0.09
	N87	−16.4 (11.9)	−39.9 to 7.2	0.2
	N88	−26.9 (7.7)	−42.2 to −11.6	< 0.001
	ND3	2.7 (6.7)	−10.6 to 16	0.7

TABLE 24 Randomised controlled trial: model-fitting results – sensitivity analyses of the primary outcome (*continued*)

Model	Covariate	Estimate (SE)	95% CI	*p*-value
	SP3	7.13 (8.5)	−9.6 to 23.9	0.4
	Gestation ≥ 26 weeks	1.3 (3.5)	−5.7 to 8.2	0.7
RSD = 16.1				
Linear regression with interaction between time to first sensor glucose and treatment	Intercept	82.6 (5.7)	71.3 to 93.9	< 0.001
	CGM vs. standard	9.5 (6.8)	−4 to 23	0.2
	Time from birth (hours) to first sensor glucose measurement	0.04 (0.18)	−0.32 to 0.41	0.8
	First sensor glucose measurement (mmol/l)	−2.3 (0.56)	−3.4 to −1.2	< 0.001
	N36 (reference N01)	−12.8 (12.4)	−37.4 to 11.7	0.3
	N42	2.7 (6.1)	−9.4 to 14.8	0.7
	N43	−0.007 (4.1)	−8 to 8	0.999
	N68	−2.8 (4.2)	−11 to 5.5	0.5
	N73	−0.5 (5.3)	−11 to 10.1	0.9
	N74	4.0 (12.4)	−20.5 to 28.5	0.7
	N85	4.9 (6.6)	−8.2 to 18	0.5
	N86	−14.6 (8.6)	−31.7 to 2.4	0.09
	N87	−17 (12)	−40 to 7	0.2
	N88	−27 (8)	−42.7 to −11.2	< 0.001
	ND3	2.7 (6.8)	−10.6 to 16	0.7
	SP3	7.1 (8.5)	−9.7 to 23.9	0.4
	Gestation ≥ 26 weeks	1.3 (3.5)	−5.7 to 8.2	0.7
	Treatment effect modification [CGM – Standard : time from birth (hours) to first sensor glucose measurement]	−0.02 (0.24)	−0.49 to 0.47	0.95
RSD = 16.2				
Linear regression with interaction between first sensor glucose measurement and treatment	Intercept	80 (4.6)	70.8 to 89.1	< 0.001
	CGM vs. standard	10.3 (2.6)	5.2 to 15.5	< 0.001
	First sensor glucose measurement (mmol/l)	−3.59 (0.67)	−4.82 to −2.16	< 0.001
	Time from birth (hours) to first sensor glucose measurement	0.06 (0.13)	−0.20 to 0.31	0.6
	N36 (reference N01)	−12 (12)	−35 to 12	0.3
	N42	1.8 (5.9)	−9.8 to 13.4	0.8
	N43	0.8 (3.9)	−7 to 8.6	0.8
	N68	−2.6 (4.1)	−10.6 to 5.5	0.5
	N73	−0.2 (5.2)	−10.4 to 10	0.97
	N74	2.7 (11.9)	−20.8 to 26.1	0.8
	N85	4.8 (6.4)	−7.97 to 17.5	0.5
	N86	−19.1 (8.5)	−35.9 to −2.4	0.03

TABLE 24 Randomised controlled trial: model-fitting results – sensitivity analyses of the primary outcome (*continued*)

Model	Covariate	Estimate (SE)	95% CI	*p*-value
	N87	−16.8 (11.6)	−39.7 to 6.1	0.1
	N88	−27.1 (7.5)	−42 to −12.2	< 0.001
	ND3	3.1 (6.5)	−9.8 to 16.1	0.6
	SP3	5.6 (8.3)	−10.7 to 21.9	0.5
	Gestation ≥ 26 weeks	3.4 (3.5)	−3.5 to 10.3	0.3
	Treatment effect modification [CGM – Standard : first sensor glucose measurement (mmol/l)]	3.1 (1)	1 to 5.1	0.004
RSD = 15.7				
Generalised least squares regression allowing for heteroscedastic variances between treatment groups	Intercept	81.9 (3.4)	75.2 to 88.7	< 0.001
	CGM vs. standard	8.9 (2.7)	3.6 to 14.2	0.001
	N36 (reference N01)	2.9 (9.4)	−15.5 to 21.3	0.8
	N42	8.3 (5.2)	−1.8 to 18.4	0.1
	N43	3.9 (3.3)	−2.6 to 10.3	0.2
	N68	−0.08 (3.2)	−6.4 to 6.2	0.98
	N73	4.7 (4.2)	−3.6 to 13	0.3
	N74	9.2 (9.4)	−9.2 to 27.6	0.3
	N85	8.5 (5.5)	−2.3 to 19.2	0.1
	N86	−23.2 (8.2)	−39.2 to −7.3	0.005
	N87	−11.8 (15.7)	−42.5 to 18.9	0.5
	N88	−12.2 (6.5)	−25 to 0.5	0.06
	ND3	7.3 (5.5)	−3.5 to 18.1	0.2
	SP3	9 (6.8)	−4.3 to 22.3	0.2
	Gestation ≥ 26 weeks	1.5 (2.9)	−4.2 to 7.3	0.6
RSD = 9.6				
Random intercept for site	Intercept	79.5 (4.1)	71.3 to 87.7	< 0.001
	CGM vs. standard	9.3 (2.8)	3.8 to 14.8	0.001
	Gestation ≥ 26 weeks	5.2 (3.6)	−1.8 to 12.2	0.1
RSD = 17.2				
Linear regression adjusting for gestation only	Intercept	80.1 (3.5)	73.3 to 86.9	< 0.001
	CGM vs. standard	9.4 (2.9)	3.7 to 15.1	0.001
	Gestation ≥ 26 weeks	5.3 (3.6)	−1.9 to 12.4	0.1
RSD = 17.8				

RSD, residual error standard deviation.
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TABLE 25 Randomised controlled trial: model-fitting results – per-protocol analysis of the primary outcome

Outcome	Covariate	Estimate (SE)	95% CI	p-value
Percentage of time sensor glucose is in the target range 2.6–10 mmol/l	Intercept	79.3 (4)	71.3 to 87.2	< 0.001
	CGM vs. standard	10.1 (3.3)	3.7 to 16.6	0.002
	N36 (reference N01)	−19 (18)	−54 to 15	0.3
	N42	9.4 (6.4)	−3.3 to 22	0.1
	N43	0.7 (4.7)	−8.6 to 9.9	0.9
	N68	5.47 (4.54)	−3.53 to 14.5	0.2
	N73	−3.4 (7.1)	−17.5 to 10.6	0.6
	N74	11 (13)	−14 to 36	0.4
	N85	8.5 (9.1)	−9.6 to 26.6	0.4
	N86	−23 (10)	−44 to −3	0.03
	N87	−11 (13)	−35 to 14	0.4
	N88	−27.7 (8.2)	−43.9 to −11.5	< 0.001
	ND3	8 (9.2)	−10.1 to 26.2	0.4
	SP3	16 (13)	−9 to 41	0.2
	Gestation ≥ 26 weeks	4.3 (3.9)	−3.5 to 12.2	0.3

RSD = 17.2

RSD, residual error standard deviation.

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome

Subgroup	Covariate	Estimate (SE)	95% CI	p-value
Site	Intercept	82.7 (4.2)	74.3 to 91	< 0.001
	CGM vs. standard	5.8 (4.7)	−3.6 to 15.1	0.2
	N36 (reference N01)	−23 (17)	−57 to 11	0.2
	N42	7 (7.2)	−7.3 to 21.1	0.3
	N43	−4.2 (5.7)	−15.6 to 7.1	0.5
	N68	1.3 (5.7)	−10 to 12.7	0.8
	N73	−4.8 (7.6)	−19.9 to 10.3	0.5
	N74	13 (17)	−21 to 47	0.4
	N85	8.7 (9.1)	−9.3 to 26.6	0.3
	N86	−10.8 (10.3)	−31.3 to 9.6	0.3
	N87	−14 (12)	−38 to 11	0.3
	N88	−47 (10)	−68 to −27	< 0.001
	ND3	7.2 (9.1)	−10.7 to 25.1	0.4
	SP3	12 (12)	−12 to 37	0.3
	Gestation ≥ 26 weeks	4.2 (3.6)	−2.9 to 11.3	0.2

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome (*continued*)

Subgroup	Covariate	Estimate (SE)	95% CI	*p*-value
	[CGM – treatment : N36 (reference N01) – site]	30 (24)	–18 to 78	0.2
	[CGM – treatment : N42 – site]	0.4 (13)	–25 to 25	0.97
	[CGM – treatment : N43 – site]	9.6 (8.4)	–6.9 to 26.2	0.3
	[CGM – treatment : N68 – site]	–2.2 (8.2)	–18.5 to 14.1	0.8
	[CGM – treatment : N73 – site]	10.6 (10.8)	–10.8 to 32.1	0.3
	[CGM – treatment : N74 – site]	–6 (24)	–54 to 42	0.8
	[CGM – treatment : N85 – site]	–1 (14)	–29 to 26	0.9
	[CGM – treatment : N86 – site]	–23 (20)	–62 to 17	0.3
	[CGM – treatment : N88 – site]	46 (16)	14 to 77	0.006
	[CGM – treatment : ND3 – site]	–0.9 (14)	–28 to 26	0.95
	[CGM – treatment : SP3 – site]	–5 (18)	–40 to 30	0.8
	[CGM – treatment : N87 – site]		n/a to n/a	
RSD = 16.9				
Sex	Intercept	86.8 (4.1)	78.6 to 94.9	< 0.001
	CGM vs. standard	2.3 (3.9)	–5.4 to 10	0.6
	Male vs. female	–11.3 (3.7)	–18.7 to –3.9	0.003
	N36 (reference N01)	–11 (12)	–35 to 13	0.4
	N42	5.7 (5.8)	–5.8 to 17.2	0.3
	N43	–0.7 (4.1)	–8.9 to 7.5	0.9
	N68	1.1 (4.1)	–7 to 9.2	0.8
	N73	–0.1 (5.4)	–10.9 to 10.6	0.98
	N74	12 (12)	–12 to 36	0.3
	N85	9.6 (6.7)	–3.7 to 22.9	0.2
	N86	–17.5 (8.7)	–34.8 to –0.3	0.05
	N87	–13 (12)	–36 to 11	0.3
	N88	–28.2 (7.8)	–43.6 to –12.8	< 0.001
	ND3	7.9 (6.8)	–5.5 to 21.4	0.2
	SP3	6.9 (8.8)	–10.5 to 24.2	0.4
	Gestation ≥ 26 weeks	4.8 (3.5)	–2.1 to 11.7	0.2
	[CGM – treatment : Male – sex]	12.6 (5.5)	1.8 to 23.5	0.02
RSD = 16.6				
Sex[a]	Intercept	86.8 (4.1)	78.6 to 94.9	< 0.001
	Male vs. female	–11.3 (3.7)	–18.7 to –3.9	0.003
	N36 (reference N01)	–11 (12)	–35 to 13	0.4
	N42	5.7 (5.8)	–5.8 to 17.2	0.3
	N43	–0.7 (4.1)	–8.9 to 7.5	0.9
	N68	1.1 (4.1)	–7 to 9.2	0.8

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome (*continued*)

Subgroup	Covariate	Estimate (SE)	95% CI	*p*-value
	N73	−0.1 (5.4)	−10.9 to 10.6	0.98
	N74	12 (12)	−12 to 36	0.3
	N85	9.6 (6.7)	−3.7 to 22.9	0.2
	N86	−17.5 (8.7)	−34.8 to −0.3	0.05
	N87	−13 (12)	−36 to 11	0.3
	N88	−28.2 (7.8)	−43.6 to −12.8	< 0.001
	ND3	7.9 (6.8)	−5.5 to 21.4	0.2
	SP3	6.9 (8.8)	−10.5 to 24.2	0.4
	Gestation ≥ 26 weeks	4.8 (3.5)	−2.1 to 11.7	0.2
	[Female – sex : CGM – treatment]	2.3 (3.9)	−5.4 to 10	0.6
	[Male – sex : CGM – treatment]	14.9 (3.8)	7.4 to 22.5	< 0.001
RSD = 16.6				
Sex (interaction with first sensor glucose measurement and treatment)	Intercept	89.2 (4)	81.3 to 97.2	< 0.001
	CGM vs. standard	2.9 (3.6)	−4.2 to 10	0.4
	Male vs. female	−11.7 (3.4)	−18.4 to −4.9	< 0.001
	First sensor glucose measurement (mmol/l)	−1.23 (0.98)	−3.16 to 0.7	0.2
	N36 (reference N01)	−13 (11)	−35 to 9	0.2
	N42	1.9 (5.3)	−8.7 to 12.4	0.7
	N43	−0.6 (3.8)	−8.1 to 6.8	0.9
	N68	−2.1 (3.8)	−9.6 to 5.4	0.6
	N73	0.2 (5)	−9.6 to 10	0.97
	N74	5 (11)	−18 to 25	0.8
	N85	4.1 (6.2)	−8.2 to 16.3	0.5
	N86	−19 (8.1)	−35.1 to −3	0.02
	N87	−17 (11)	−38 to 5	0.1
	N88	−28.5 (7.2)	−42.6 to −14.3	< 0.001
	ND3	3.6 (6.3)	−8.9 to 16.1	0.6
	SP3	5.1 (8)	−10.6 to 20.9	0.5
	Gestation ≥ 26 weeks	2.2 (3.4)	−4.5 to 8.9	0.5
	[CGM – treatment : Male – sex]	13.2 (5)	3.2 to 23.1	0.01
	[CGM – treatment : First sensor glucose measurement]	0.6 (1.4)	−2.2 to 3.4	0.7
	[Male – sex : First sensor glucose measurement]	−3.8 (1.3)	−6.3 to −1.2	0.004
	[CGM – treatment : Male – sex : First sensor glucose measurement]	3.8 (2)	−0.07 to 7.7	0.05

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome (*continued*)

Subgroup	Covariate	Estimate (SE)	95% CI	*p*-value
RSD = 15				
Corrected gestational age	Intercept	111 (13)	85 to 137	< 0.001
	CGM vs. standard	−9 (19)	−46 to 28	0.6
	Corrected age	109 (52)	6 to 211	0.04
	N36 (reference N01)	−9 (12)	−32 to 16	0.5
	N42	6.9 (6)	−5.1 to 18.8	0.3
	N43	0.6 (4.2)	−7.7 to 8.9	0.9
	N68	0.6 (4.2)	−7.6 to 8.9	0.9
	N73	−1.4 (5.6)	−12.5 to 9.7	0.8
	N74	9.4 (12.3)	−14.9 to 33.6	0.4
	N85	7.7 (6.9)	−6 to 21.3	0.3
	N86	−17.7 (8.9)	−35.3 to −0.01	0.05
	N87	−12 (12)	−36 to 13	0.4
	N88	−30.8 (8.1)	−46.8 to −14.8	< 0.001
	ND3	6 (6.9)	−7.6 to 19.6	0.4
	SP3	8.9 (8.9)	−8.7 to 26.4	0.3
	[CGM – treatment : corrected age]	−72 (76)	−223 to 79	0.4
RSD = 16.9				
Birthweight SDS	Intercept	83.6 (3.9)	75.8 to 91.3	< 0.001
	CGM vs. standard	5.4 (3.7)	−1.9 to 12.6	0.1
	Weight SDS	5.3 (2.1)	1 to 9.5	0.02
	N36 (reference N01)	−4 (12)	−28 to 20	0.8
	N42	6.3 (5.9)	−5.4 to 18.1	0.3
	N43	−0.6 (4.2)	−9 to 7.6	0.9
	N68	−0.4 (4.1)	−8.6 to 7.8	0.9
	N73	2 (5.5)	−8.8 to 12.8	0.7
	N74	8 (12)	−16 to 32	0.5
	N85	8.9 (6.8)	−4.5 to 22.3	0.2
	N86	−13.9 (8.8)	−31.4 to 3.5	0.1
	N87	−20 (13)	−44 to 5	0.1
	N88	−29.3 (8.1)	−45.3 to −13.3	< 0.001
	ND3	6.7 (6.8)	−6.7 to 20.1	0.3
	SP3	9.5 (8.9)	−8.1 to 27.1	0.3
	Gestation ≥ 26 weeks	6.6 (3.6)	−0.5 to 13.7	0.07
	[CGM – treatment : weight SDS]	−4.2 (3.1)	−10.4 to 2	0.2

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome (*continued*)

Subgroup	Covariate	Estimate (SE)	95% CI	*p*-value
RSD = 16.8				
Antenatal steroids	Intercept	81.4 (3.9)	73.7 to 89	< 0.001
	CGM vs. standard	7.5 (3.2)	1.2 to 13.9	0.02
	Antenatal steroids (no vs. yes)	−2.8 (4.7)	−12 to 6.4	0.5
	N36 (reference N01)	−6 (13)	−31 to 19	0.6
	N42	8.3 (6.2)	−4 to 20.5	0.2
	N43	0.4 (4.6)	−8.6 to 9.5	0.9
	N68	0.5 (4.2)	−7.9 to 8.9	0.9
	N73	−0.08 (5.6)	−11.1 to 11	0.99
	N74	12 (13)	−13 to 37	0.4
	N85	9.4 (7.2)	−4.8 to 23.6	0.2
	N86	−15.5 (9)	−33.3 to 2.3	0.09
	N87	−13 (12)	−37 to 12	0.3
	N88	−28.5 (8.1)	−44.4 to −12.6	< 0.001
	ND3	7.3 (7.1)	−6.7 to 21.2	0.3
	SP3	9 (9)	−8.9 to 26.8	0.3
	Gestation ≥ 26 weeks	4.7 (3.7)	−2.5 to 11.9	0.2
	[CGM – treatment : No – antenatal steroids]	6 (7)	−8 to 19.9	0.4
RSD = 17.1				
Maternal chorioamnionitis	Intercept	80.6 (4.9)	70.9 to 90.3	< 0.001
	CGM vs. standard	10.8 (5.7)	−0.5 to 22.1	0.06
	Maternal chorioamnionitis (no vs. yes)	−0.4 (4.6)	−9.6 to 8.8	0.9
	Maternal chorioamnionitis (unknown vs. yes)	15 (13)	−11 to 40	0.3
	N36 (reference N01)	−7 (12)	−32 to 18	0.6
	N42	8 (6)	−3.8 to 19.8	0.2
	N43	0.6 (4.3)	−8 to 9.1	0.9
	N68	0.4 (4.3)	−8.2 to 8.9	0.9
	N73	0.6 (5.6)	−10.5 to 11.7	0.9
	N74	11 (12)	−14 to 36	0.4
	N85	8.3 (7)	−5.6 to 22.1	0.2
	N86	−15.2 (9.1)	−33.1 to 2.7	0.1
	N87	−12 (13)	−37 to 13	0.3
	N88	−28.4 (8.2)	−44.6 to −12.3	< 0.001
	ND3	7.3 (7)	−6.5 to 21.1	0.3
	SP3	9.7 (9)	−8.1 to 27.6	0.3

TABLE 26 Randomised controlled trial: model-fitting results – subgroup analyses of the primary outcome (*continued*)

Subgroup	Covariate	Estimate (SE)	95% CI	*p*-value
	Gestation ≥ 26 weeks	4.5 (3.7)	–2.7 to 11.8	0.2
	[CGM – treatment : No – maternal chorioamnionitis]	–2.1 (6.7)	–15.3 to 11.1	0.8
	[CGM – treatment : Unknown – maternal chorioamnionitis]	–19 (18)	–55 to 18	0.3
RSD = 17.2				
Maternal diabetes	Intercept	78.7 (7.4)	64 to 93.4	< 0.001
	CGM vs. standard	13 (11)	–8 to 34	0.2
	Maternal diabetes (no vs. yes)	2.1 (6.8)	–11.2 to 15.5	0.8
	N36 (reference N01)	–8 (12)	–33 to 17	0.5
	N42	7.7 (6)	–4.1 to 19.4	0.2
	N43	0.2 (4.3)	–8.3 to 8.6	0.97
	N68	–0.1 (4.3)	–8.6 to 8.3	0.98
	N73	0.2 (5.6)	–10.8 to 11.2	0.97
	N74	10 (12)	–15 to 34	0.4
	N85	8.3 (7.2)	–5.8 to 22.5	0.2
	N86	–16.2 (9)	–34 to 1.6	0.08
	N87	–12 (13)	–37 to 12	0.3
	N88	–28.7 (8.1)	–44.7 to –12.7	< 0.001
	ND3	6.8 (7)	–7 to 20.5	0.3
	SP3	9.5 (9)	–8.3 to 27.2	0.3
	Gestation ≥ 26 weeks	5 (3.7)	–2.2 to 12.2	0.2
	[CGM – treatment : No – maternal diabetes]	–5 (11)	–27 to 17	0.7

RSD = 17.2

n/a, not applicable; RSD, residual error standard deviation.
a   Model to investigate whether or not treatment effect differs depending on sex.

TABLE 27 Randomised controlled trial: multiple testing procedure

Test	Outcome	Nominal *p*-value	Rank	Significant
Hochberg	Percentage of time sensor glucose is in the target range 2.6–10 mmol/l	0.002	1	Yes
Hochberg	Percentage of time sensor glucose is in the target range 4–8 mmol/l	0.004	2	Yes
Hochberg	Mean sensor glucose	0.099	3	No
Gate-keeping	Sensor glucose variability (unconditional)	0.9	4	No
Gate-keeping	Percentage of time sensor glucose is in the hyperglycaemic range (> 15 mmol/l)	0.1	5	No

TABLE 28 Randomised controlled trial: withdrawals from treatment only

Subject ID	Group	Date of randomisation	Date of withdrawal	Reason	Description	Number of intervention days completed	Later withdrawn from trial?
N43-1032	Standard	26 April 2017	1 May 2017	Clinical decision			Yes
N43-1034	Standard	4 May 2017	9 May 2017	Clinical decision			No
N68-1091	Standard	1 March 2018	2 March 2018	Clinical decision		2	No
N74-1092	Standard	1 March 2018	3 March 2018	Clinical decision		2	No
N86-1131	Standard	13 July 2018	16 July 2018	Clinical decision		3	No
N87-1168	Standard	21 November 2018	28 November 2018	Clinical decision		6	No
N01-1083	Standard	5 February 2018	6 February 2018	Other	Clinical decision. Third sensor failed and inappropriate to attempt fourth sensor	2	No
N36-1021	Standard	25 January 2017	26 January 2017	Other	Sensor would not work		No
N36-1066	Standard	19 December 2017	20 December 2017	Other	Unable to get sensor to calibrate	1	No
N36-1102	Standard	28 March 2018	29 March 2018	Other	Unable to get sensor to calibrate	1	No
N42-1049	Standard	21 August 2017	27 August 2017	Other	Sensor stopped working	6	No
N68-1068	Standard	22 December 2017	25 December 2017	Other	Device-related issue	3	No
N68-1082	Standard	4 February 2018	6 February 2018	Other	Infant transferred to another hospital and so sensor was removed	2	No
N68-1107	Standard	10 April 2018	13 April 2018	Other	Transferred to another hospital for intervention	4	No
N73-1090	Standard	27 February 2018	4 March 2018	Other	Interstitial signal not recording and therefore sensor removed	5	No
N73-1164	Standard	13 November 2018	17 November 2018	Other	Infant transferred to Salisbury	5	No
N88-1151	Standard	20 September 2018	21 September 2018	Other	Joint agreement. Equipment malfunction	1	No

Subject ID	Group	Date of randomisation	Date of withdrawal	Reason	Description	Number of intervention days completed	Later withdrawn from trial?
N01-1048	CGM	21 August 2017	22 August 2017	Clinical decision		1	Yes
N36-1022	CGM	25 January 2017	26 January 2017	Clinical decision			No
N36-6022	CGM	1 November 2017	3 November 2017	Clinical decision		2	No
N43-1027	CGM	30 March 2017	31 March 2017	Clinical decision			No
N43-1028	CGM	30 March 2017	2 April 2017	Clinical decision			No
N68-1138	CGM	7 August 2018	10 August 2018	Clinical decision		3	No
N85-1175	CGM	15 January 2019	17 January 2019	Clinical decision		2	No
N01-1059	CGM	9 November 2017	11 November 2017	Other	Failed sensor. Parents did not want a replacement sensor inserted	3	No
N68-1080	CGM	1 February 2018	1 February 2018	Other	Could not get a sensor into the infant	0	No
N73-1165	CGM	14 November 2018	17 November 2018	Other	Sensor readings lost	4	No
N74-1128	CGM	23 June 2018	29 June 2018	Other	Advice from trial team because the infant was 9 days old (not 7 days) because of the delay in inserting the sensor	5	No
N88-1173	CGM	18 December 2018	19 December 2018	Other	Equipment malfunctioning. Could not get transmitters to work despite good sensor placement	2	No
SP3-1085	CGM	14 February 2018	15 February 2018	Other	Monitor not working	0	No

ID, identification.

TABLE 29 Randomised controlled trial: withdrawals from the RCT

Subject ID	Group	Date of randomisation	Date of withdrawal	Study timing	Reason	Description
N01-1052	Standard	13 October 2017	13 October 2017	Days 1–7	Parental decision	
N36-1117	Standard	22 May 2018	23 May 2018	Days 1–7	Parental decision	
ND3-1062	Standard	30 November 2017	30 November 2017	Days 1–7	Other	No sensor readings because infant was small. Inserted new sensor; still no readings
N87-1148	Standard	14 September 2018	15 September 2018	Days 8–14	Other	No interstitial signal or BMG reading on MiniMed
N01-1144	CGM	1 September 2018	1 September 2018	Days 1–7	Parental decision	
N01-1006	CGM	15 September 2016	18 September 2016	Days 8–14	Clinical decision	
N36-1033	CGM	3 May 2017	4 May 2017	Days 8–14	Clinical decision	
N73-1141	CGM	21 August 2018	22 August 2018	Days 8–14	Clinical decision	
N42-1016	CGM	8 December 2016	12 December 2016	Days 8–14	Parental decision	
N87-1142	CGM	23 August 2018	25 August 2018	Days 8–14	Parental decision	
N87-1172	CGM	16 December 2018	17 December 2018	Days 8–14	Other	Large IVH for reorientation of care. Death 18 December 2018

BG, blood glucose; ID, identification; IVH, intraventricular haemorrhage.

TABLE 30 Randomised controlled trial: listing of deaths

Subject ID	Group	Date of randomisation	Date of death	Study timing
N43-1038	Standard	29 May 2017	30 May 2017	Days 1–7
N73-1095	Standard	14 March 2018	15 March 2018	Days 1–7
N01-1147	Standard	10 September 2018	23 September 2018	Days 8–14
N36-1018	Standard	5 January 2017	2 February 2017	Post day 14
N43-1032	Standard	26 April 2017	13 May 2017	Post day 14
N68-1139	Standard	11 August 2018	26 August 2018	Post day 14
N01-1048	CGM	21 August 2017	7 October 2017	Post day 14
N01-1087	CGM	20 February 2018	10 March 2018	Post day 14

ID, identification.

TABLE 31 Randomised controlled trial: growth parameters at birth

Variable	Statistic	Standard-care arm	CGM arm	Total
Birthweight (g)	n	95	84	179
	Mean (SD)	880 (180)	910 (160)	890 (170)
	Median	920	930	930
	Minimum, maximum	470, 1170	390, 1190	390, 1190
Birthweight SDS	n	95	84	179
	Mean (SD)	−0.8 (0.92)	−0.82 (0.98)	−0.81 (0.95)
	Median	−0.66	−0.76	−0.74
	Minimum, maximum	−2.6, 1.32	−2.97, 1.2	−2.97, 1.32
Body length (cm)	n	64	55	119
	Mean (SD)	33 (2.5)	33.2 (2.8)	33 (2.6)
	Median	33	33	33
	Minimum, maximum	26, 38	24.5, 38	24.5, 38
Body length SDS	n	64	55	119
	Mean (SD)	−1.54 (0.81)	−1.56 (0.89)	−1.55 (0.84)
	Median	−1.45	−1.41	−1.41
	Minimum, maximum	−3.87, −0.41	−3.73, 0.24	−3.87, 0.24
Head circumference (cm)	n	87	75	162
	Mean (SD)	24.1 (1.9)	24.5 (1.8)	24.3 (1.9)
	Median	24.5	24.8	24.5
	Minimum, maximum	19, 28	19, 28	19, 28
Head circumference SDS	n	87	75	162
	Mean (SD)	−1.16 (0.86)	−1.12 (0.99)	−1.14 (0.92)
	Median	−1.14	−1.04	−1.1
	Minimum, maximum	−3.03, 0.82	−3.5, 1.11	−3.5, 1.11

TABLE 32 Randomised controlled trial: growth parameters at day 7

Variable	Statistic	Standard-care arm	CGM arm	Total
Weight (g)	n	87	76	163
	Mean (SD)	890 (180)	930 (160)	910 (170)
	Median	920	960	930
	Minimum, maximum	480, 1220	450, 1220	450, 1220
Weight SDS	n	87	76	163
	Mean (SD)	−1.3 (0.75)	−1.26 (0.79)	−1.28 (0.77)
	Median	−1.14	−1.19	−1.16
	Minimum, maximum	−3.11, 0.16	−3.2, 0.17	−3.2, 0.17
Body length (cm)	n	63	56	119
	Mean (SD)	33.7 (2.7)	33.8 (2.7)	33.7 (2.7)
	Median	34	34	34
	Minimum, maximum	24, 39.5	24.5, 39.3	24, 39.5
Body length SDS	n	63	56	119
	Mean (SD)	−1.81 (1.07)	−1.78 (0.87)	−1.8 (0.97)
	Median	−1.59	−1.67	−1.6
	Minimum, maximum	−7.01, 0.16	−4.19, −0.28	−7.01, 0.16
Head circumference (cm)	n	72	60	132
	Mean (SD)	24.1 (1.8)	24.4 (1.6)	24.2 (1.7)
	Median	24	24.5	24.3
	Minimum, maximum	19.7, 28	20, 27.7	19.7, 28
Head circumference SDS	n	72	60	132
	Mean (SD)	−1.84 (0.77)	−1.76 (0.83)	−1.81 (0.8)
	Median	−1.85	−1.56	−1.73
	Minimum, maximum	−3.6, 0.03	−3.91, 0.03	−3.91, 0.03

TABLE 33 Randomised controlled trial: growth parameters at day 14

Variable	Statistic	Standard-care arm	CGM arm	Total
Weight (g)	*n*	89	76	165
	Mean (SD)	980 (200)	1020 (200)	1000 (200)
	Median	980	1040	1000
	Minimum, maximum	480, 1390	530, 1380	480, 1390
Weight SDS	*n*	89	76	165
	Mean (SD)	−1.38 (0.76)	−1.39 (0.77)	−1.38 (0.76)
	Median	−1.35	−1.35	−1.35
	Minimum, maximum	−3.06, 0.21	−3.06, 0.31	−3.06, 0.31
Body length (cm)	*n*	59	51	110
	Mean (SD)	34.5 (2.6)	34.6 (2.7)	34.6 (2.6)
	Median	35	35	35
	Minimum, maximum	26.5, 40	26, 38.5	26, 40
Body length SDS	*n*	59	51	110
	Mean (SD)	−1.98 (0.88)	−1.96 (0.83)	−1.97 (0.85)
	Median	−1.93	−1.94	−1.93
	Minimum, maximum	−4.71, −0.11	−3.89, −0.56	−4.71, −0.11
Head circumference (cm)	*n*	74	66	140
	Mean (SD)	25 (2.3)	25.4 (2.4)	25.2 (2.4)
	Median	25	25.5	25.2
	Minimum, maximum	19.2, 35.6	20.5, 36.5	19.2, 36.5
Head circumference SDS	*n*	74	66	140
	Mean (SD)	−1.9 (1.1)	−1.8 (1.2)	−1.9 (1.2)
	Median	−2.1	−1.9	−1.9
	Minimum, maximum	−4.1, 3.5	−4.5, 4	−4.5, 4

TABLE 34 Randomised controlled trial: growth parameters at 36 weeks' corrected gestation

Variable	Statistic	Standard-care arm	CGM arm	Total
Weight (g)	*n*	85	75	160
	Mean (SD)	2030 (390)	2040 (360)	2030 (380)
	Median	2050	2020	2050
	Minimum, maximum	1130, 2820	1160, 2980	1130, 2980
Weight SDS	*n*	85	75	160
	Mean (SD)	−1.54 (0.94)	−1.56 (0.93)	−1.55 (0.93)
	Median	−1.47	−1.57	−1.5
	Minimum, maximum	−3.83, 0.45	−3.92, 0.65	−3.92, 0.65
Body length (cm)	*n*	41	27	68
	Mean (SD)	41.3 (3.4)	40.7 (3.9)	41.1 (3.6)
	Median	42	41	41
	Minimum, maximum	34, 47	29.6, 47	29.6, 47
Body length SDS	*n*	41	27	68
	Mean (SD)	−2.6 (1.6)	−2.9 (1.8)	−2.7 (1.6)
	Median	−2.3	−2.8	−2.6
	Minimum, maximum	−6, 0.09	−7.8, 0.03	−7.8, 0.09
Head circumference (cm)	*n*	71	59	130
	Mean (SD)	30.9 (2.1)	31.2 (2.2)	31 (2.1)
	Median	30.8	31	30.9
	Minimum, maximum	25.6, 36	26.5, 39.7	25.6, 39.7
Head circumference SDS	*n*	71	59	130
	Mean (SD)	−1.3 (1.6)	−1.1 (1.7)	−1.2 (1.6)
	Median	−1.4	−1.3	−1.3
	Minimum, maximum	−5.5, 2.8	−4.8, 5.6	−5.5, 5.6

TABLE 35 Randomised controlled trial: completeness of data used for health economic evaluation

Data	Item	CGM arm (N = 84), n (%)				Standard-care arm (N = 95), n (%)				Total (N = 179), n (%)			
		Completed	CRF not available	CRF not applicable	Data on variable missing	Completed	CRF not available	CRF not applicable	Data on variable missing	Completed	CRF not available	CRF not applicable	Data on variable missing
Enlite sensor (MiniMed system)	MiniMed 640G 3.0-ml insulin pump	81 (96)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	81 (45)	0 (0)	98 (55)	0 (0)
	Guardian 2 Link	81 (96)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	91 (45)	0 (0)	98 (55)	0 (0)
	Generation Enlite single sensor: MMT-7008B	81 (96)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	91 (45)	0 (0)	98 (55)	0 (0)
Glucose monitoring	Glucose sensor insertion	81 (96)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	81 (45)	0 (0)	98 (55)	0 (0)
	Glucose sensor monitoring	75 (89)	6 (7)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	75 (42)	6 (3)	98 (55)	0 (0)
	Glucose sensor removal	81 (96)	0 (0)	3 (4)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	81 (45)	0 (0)	98 (55)	0 (0)
POC testing used to calibrate MiniMed 640G	Nova StatStrip meter	75 (89)	0 (0)	9 (11)	0 (0)	93 (98)	0 (0)	2 (2)	0 (0)	168 (94)	0 (0)	11 (6)	0 (0)
Length of stay	Total: days 1–7	83 (99)	1 (1)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	177 (99)	2 (1)	0 (0)	0 (0)
	Total: randomisation to 36 weeks	73 (87)	11 (13)	0 (0)	0 (0)	83 (87)	12 (13)	0 (0)	0 (0)	156 (87)	23 (13)	0 (0)	0 (0)
Medication	Any medication use: days 1–7	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Inotrope use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Antibiotic use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Caffeine use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Morphine use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Corticosteroid use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Insulin use	81 (96)	3 (4)	0 (0)	0 (0)	94 (99)	1 (1)	0 (0)	0 (0)	175 (98)	4 (2)	0 (0)	0 (0)
	Insulin use over post-intervention period	77 (92)	7 (8)	0 (0)	0 (0)	89 (94)	6 (6)	0 (0)	0 (0)	166 (93)	13 (7)	0 (0)	0 (0)

TABLE 35 Randomised controlled trial: completeness of data used for health economic evaluation (*continued*)

Data	Item	CGM arm (N = 84), n (%)				Standard-care arm (N = 95), n (%)				Total (N = 179), n (%)			
		Completed	CRF not available	CRF not applicable	Data on variable missing	Completed	CRF not available	CRF not applicable	Data on variable missing	Completed	CRF not available	CRF not applicable	Data on variable missing
Investigations	Any investigation use	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Cranial ultrasound	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Other ultrasound	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	CT	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	X-ray	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	EEG	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	MRI	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Echocardiography	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	ECG	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
Blood transfusion products	Any product use	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Fresh-frozen plasma	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Red blood cells	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Platelets	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
Medical treatment	Any medical treatment use	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Lumbar puncture	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Ventricular tap	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Long line	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
Surgical procedures	Any surgical procedure use	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Ventriculoperitoneal shunts	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Surgical procedures for central access	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
	Interventions for ROP treatment	74 (88)	10 (12)	0 (0)	0 (0)	85 (89)	10 (11)	0 (0)	0 (0)	159 (89)	20 (11)	0 (0)	0 (0)
Mode of discharge if infant is transferred to another hospital (n = 75)[a]		38 (100)	0 (0)	0 (0)	0 (0)	37 (100)	0 (0)	0 (0)	0 (0)	75 (100)	0 (0)	0 (0)	0 (0)

a Total number transferred to another hospital.

EME
HS&DR
HTA
PGfAR
PHR